

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ :		A2	(11) International Publication Number: WO 95/01348
C07D 401/04, 401/211, 401/209, 471/04, 471/221, 471/209, A61K 31/33, C07D 211/88, 209/48, 403/06, 403/233, 403/209, 209/46, 213/55, C07C 229/34, C07D 401/06, 401/213, 401/209, 209/48, 209/76, 209/48			(43) International Publication Date: 12 January 1995 (12.01.95)
(21) International Application Number: PCT/US94/07411		(81) Designated States: AU, CA, CZ, FI, HU, JP, KR, NZ, PL, RU, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
(22) International Filing Date: 1 July 1994 (01.07.94)		Published <i>Without international search report and to be republished upon receipt of that report.</i>	
(30) Priority Data: 08/087,510 2 July 1993 (02.07.93) US			
(71) Applicant (for all designated States except US): CELGENE CORPORATION [US/US]; 7 Powder Horn Drive, Warren, NJ 07059 (US).			
(71)(72) Applicant and Inventor: MULLER, George, W. [US/US]; 250 Windmill Court, Bridgewater, NJ (US).			
(74) Agents: NISSIM, Stuart, H. et al.; Matthews, Woodbridge & Collins, Suite 306, 100 Thanet Circle, Princeton, NJ 08540-3662 (US).			

(54) Title: IMIDES AS INHIBITORS OF TNP ALPHA

(57) Abstract

Cyclic imides are inhibitors of tumor necrosis factor α and can be used to combat cachexia, endotoxic shock, and retrovirus replication. A typical embodiment is methyl [3-phthalimido-3-(3,4-dimethoxyphenyl)]propionate.

Atty Docket#: 9516-078
Serial #: 10/693,722
Reference: A95

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

IMIDES AS INHIBITORS OF TNF ALPHA

Background of the Invention

5 The present invention relates a method of reducing levels of TNF α in a mammal and to compounds and compositions useful therein.

10 TNF α , or tumor necrosis factor α , is a cytokine which is released primarily by mononuclear phagocytes in response to various immunostimulators. When administered to animals or humans it causes inflammation, fever, cardiovascular effects, hemorrhage, coagulation and acute phase responses similar to those seen during acute infections and shock states.

15 Excessive or unregulated TNF α production has been implicated in a number of disease conditions. These include endotoxemia and/or toxic shock syndrome (Tracey et al., Nature 330, 662-664 (1987) and Hinshaw et al., Circ. Shock 30, 279-292 (1990)); cachexia (Dezube et al., Lancet, 335 (8690), 662 (1990)); and Adult Respiratory Distress Syndrome where TNF α concentration in excess of 12,000 pg/mL have been detected in 20 pulmonary aspirates from ARDS patients (Millar et al., Lancet 2(8665), 712-714 (1989)). Systemic infusion of recombinant TNF α also resulted in changes typically seen in ARDS (Ferrai-Baliviera et al., Arch. Surg. 124(12), 1400-1405 (1989)).

25 TNF α appears to be involved in bone resorption diseases, including arthritis where it has been determined that when activated, leukocytes will produce a bone-resorbing activity, and data suggest that TNF α contributes to this activity. (Bertolini et al., Nature 319, 516-518 (1986) and Johnson et al., Endocrinology 124(3), 1424-1427 (1989).) It has been determined that TNF α stimulates bone resorption and inhibits 30 bone formation in vitro and in vivo through stimulation of osteoclast formation and activation combined with inhibition of osteoblast function. Although TNF α may be involved in many

5 bone resorption diseases, including arthritis, the most compelling link with disease is the association between production of TNF α by tumor or host tissues and malignancy associated hypercalcemia (Calci. Tissue Int. (US) 46(Suppl.), S3-10 (1990)). In Graft versus Host Reaction, increased serum TNF α levels have been associated with major complication following acute allogenic bone marrow transplants (Holler et al., Blood, 75(4), 1011-1016 (1990)).

10 Cerebral malaria is a lethal hyperacute neurological syndrome associated with high blood levels of TNF α and the most severe complication occurring in malaria patients. Levels of serum TNF α correlated directly with the severity of disease and the prognosis in patients with acute malaria attacks (Grau et al., N. Engl. J. Med. 320(24), 1586-1591 (1989)).

15 TNF α also plays a role in the area of chronic pulmonary inflammatory diseases. The deposition of silica particles leads to silicosis, a disease of progressive respiratory failure caused by a fibrotic reaction. Antibody to TNF α completely blocked the silica-induced lung fibrosis in mice (Pignet et al., Nature, 344:245-247 (1990)). High levels of TNF α production (in the serum and in isolated macrophages) have been demonstrated in animal models of silica and asbestos induced fibrosis (Bissonnette et al., Inflammation 13(3), 329-339 (1989)). Alveolar macrophages from pulmonary sarcoidosis 20 patients have also been found to spontaneously release massive quantities of TNF α as compared with macrophages from normal donors (Baughman et al., J. Lab. Clin. Med. 115(1), 36-42 (1990)).

30 TNF α is also implicated in the inflammatory response which follows reperfusion, called reperfusion injury, and is a major cause of tissue damage after loss of blood flow (Vedder et al., PNAS 87, 2643-2646 (1990)). TNF α also alters the properties of endothelial cells and has various pro-coagulant 35 activities, such as producing an increase in tissue factor pro-coagulant activity and suppression of the anticoagulant

protein C pathway as well as down-regulating the expression of thrombomodulin (Sherry et al., *J. Cell Biol.* **107**, 1269-1277 (1988)). TNF α has pro-inflammatory activities which together with its early production (during the initial stage of an inflammatory event) make it a likely mediator of tissue injury in several important disorders including but not limited to, myocardial infarction, stroke and circulatory shock. Of specific importance may be TNF α -induced expression of adhesion molecules, such as intercellular adhesion molecule (ICAM) or endothelial leukocyte adhesion molecule (ELAM) on endothelial cells (Munro et al., *Am. J. Path.* **135**(1), 121-132 (1989)).

Moreover, it now is known that TNF α is a potent activator of retrovirus replication including activation of HIV-1. (Duh et al., *Proc. Nat. Acad. Sci.* **86**, 5974-5978 (1989); Poll et al., *Proc. Nat. Acad. Sci.* **87**, 782-785 (1990); Monto et al., *Blood* **79**, 2670 (1990); Clouse et al., *J. Immunol.* **142**, 431-438 (1989); Poll et al., *AIDS Res. Hum. Retrovirus*, 191-197 (1992)). AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified, i.e., HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Other viruses, such as HIV-1, HIV-2 infect T lymphocytes after T cell activation and such virus protein expression and/or replication is mediated or maintained by such T cell activation. Once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication. Cytokines, specifically TNF α , are implicated in activated T-cell mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with cytokine activity such as by prevention or inhibition of cytokine production, notably TNF α , in an HIV-infected individual aids in limiting the maintenance of T lymphocyte caused by HIV infection.

Monocytes, macrophages, and related cells, such as kupffer and glial cells, have also been implicated in maintenance of the HIV infection. These cells, like T cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. (Rosenberg et al., The Immunopathogenesis of HIV Infection, Advances in Immunology, 57 (1989)). Cytokines, such as TNF_α , have been shown to activate HIV replication in monocytes and/or macrophages (Poli et al. Proc. Natl. Acad. Sci., 87, 782-784 (1990)), therefore, prevention or inhibition of cytokine production or activity aids in limiting HIV progression as stated above for T cells. Additional studies have identified TNF_α as a common factor in the activation of HIV in vitro and has provided a clear mechanism of action via a nuclear regulatory protein found in the cytoplasm of cells (Osborn, et al., PNAS 86 2336-2340). This evidence suggests that a reduction of TNF_α synthesis may have an antiviral effect in HIV infections, by reducing the transcription and thus virus production.

AIDS viral replication of latent HIV in T cell and macrophage lines can be induced by TNF_α (Folks et al., PNAS 86, 2365-2368 (1989)). A molecular mechanism for the virus inducing activity is suggested by TNF_α 's ability to activate a gene regulatory protein (NFKB) found in the cytoplasm of cells, which promotes HIV replication through binding to a viral regulatory gene sequence (LTR) (Osborn et al., PNAS 86, 2336-2340 (1989)). TNF_α in AIDS associated cachexia is suggested by elevated serum TNF_α and high levels of spontaneous TNF_α production in peripheral blood monocytes from patients (Wright et al. J. Immunol. 141(1), 99-104 (1988)).

TNF_α has been implicated in various roles with other viral infections, such as the cytomegalia virus (CMV), influenza virus, adenovirus, and the herpes family of viruses for similar reasons as those noted.

35 Preventing or inhibiting the production or action of TNF_α is, therefore, predicted to be a potent therapeutic strategy

for many inflammatory, infectious, immunological or malignant diseases. These include but are not restricted to septic shock, sepsis, endotoxic shock, hemodynamic shock and sepsis syndrome, post ischemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic disease, cachexia, graft rejection, cancer, autoimmune disease, opportunistic infections in AIDS, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, other arthritic conditions, Crohn's disease, ulcerative colitis, multiple sclerosis, systemic lupus erythrematosis, ENL in leprosy, radiation damage, and hyperoxic alveolar injury. Efforts directed to the suppression of the effects of TNF α have ranged from the utilization of steroids such as dexamethasone and prednisolone to the use of both polyclonal and monoclonal antibodies (Beutler et al., Science 234, 470-474 (1985); WO 92/11383).

The nuclear factor kB (NFKB) is a pleiotropic transcriptional activator (Lenardo, et al. Cell 1989, 58, 227-29). NFKB has been implicated as a transcriptional activator in a variety of disease and inflammatory states and is thought to regulate cytokine levels including but not limited to TNF α and also to be an activator of HIV transcription (Dbaibo, et al. J. Biol. Chem. 1993, 17762-66; Duh et al. Proc. Natl. Acad. Sci. 1989, 86, 5974-78; Bachelerie et al. Nature 1991, 350, 709-12; Boswas et al. J. Acquired Immune Deficiency Syndrome 1993, 6, 778-786; Suzuki et al. Biochem. And Biophys. Res. Comm. 1993, 193, 277-83; Suzuki et al. Biochem. And Biophys. Res Comm. 1992, 189, 1709-15; Suzuki et al. Biochem. Mol. Bio. Int. 1993, 31(4), 693-700; Shakhov et al. 1990, 171, 35-47; and Staal et al. Proc. Natl. Acad. Sci. USA 1990, 87, 9943-47). Thus, inhibition of NFKB binding can regulate transcription of cytokine gene(s) and through this modulation and other mechanisms be useful in the inhibition of a multitude of disease states. The compounds claimed in this patent can inhibit the action of NFKB in the nucleus and thus are useful in the treatment of a variety of diseases including but not limited to rheumatoid arthritis, rheumatoid spondylitis, osteo-

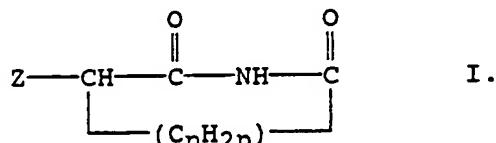
5 arthritis, other arthritic conditions, septic shock, sepsis, endotoxic shock, graft versus host disease, wasting, Crohn's disease, ulcerative colitis, multiple sclerosis, systemic lupus erythematosus, ENL in leprosy, HIV, AIDS, and opportunistic infections in AIDS.

TNF α and NFKB levels are influenced by a reciprocal feedback loop. As noted above, the compounds of the present invention affect the levels of both TNF α and NFKB. It is not known at this time, however, how the compounds of the present invention regulate the levels of TNF α , NFKB, or both.

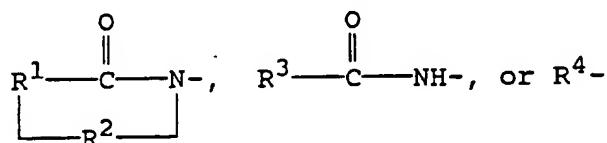
Detailed Description

The present invention is based on the discovery that a class of non-polypeptide imides more fully described herein appear to inhibit the action of TNF α .

15 A first aspect of the present invention pertains to
compounds of the formula:



in which z is



30 in which

R^1 is the divalent residue of (i) 3,4-pyridine, (ii) pyrrolidine, (iii) imidizole, (iv) naphthalene, (v) thiophene, or (vi) a straight or branched alkane of 2 to 6 carbon atoms, unsubstituted or substituted with phenyl or phenyl substituted with nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy,

carbopropoxy, acetyl, carbamyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, wherein the divalent bonds of said residue are on vicinal ring carbon atoms;

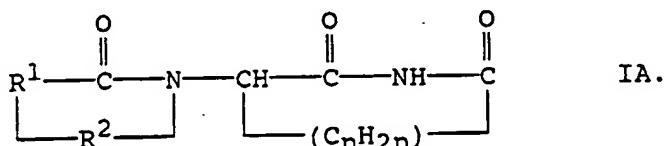
5 R² is -CO- or -SO₂-;

R³ is (i) phenyl substituted with 1 to 3 substituents each selected independently from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, (ii) pyridyl, (iii) pyrrolyl, (iv) imidazolyl, (v) naphthyl, (vi) thienyl, (vii) quinolyl, (viii) furyl, or (ix) indolyl;

15 R⁴ is alanyl, arginyl, glycyl, phenylglycyl, histidyl, leucyl, isoleucyl, lysyl, methionyl, prolyl, sarcosyl, seryl, homoseryl, threonyl, thryonyl, tyrosyl, valyl, benzimidol-2-yl, benzoxazol-2-yl, phenylsulfonyl, methylphenylsulfonyl, or phenylcarbamoyl; and

n has a value of 1, 2, or 3.

More particularly, a first preferred subclass pertains to compounds of the formula:

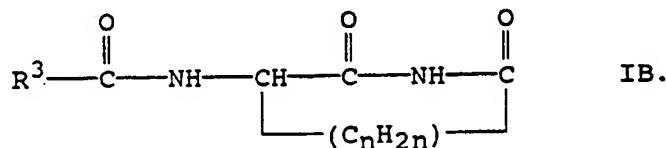


in which R¹ is the divalent residue of (i) 3,4-pyridine,
(ii) pyrrolidine, (iii) imidazole, (iv) naphthalene, (v) thiophene, or (vi) a straight or branched alkane of 2 to 6 carbon atoms, unsubstituted or substituted with phenyl or phenyl substituted with nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, wherein the divalent bonds of said

residue are on vicinal ring carbon atoms; R² is -CO- or -SO₂-; and n has a value of 1, 2, or 3.

Preferred compounds of Formula IA include those in which R¹ is a divalent residue of pyridine, naphthalene or imidazole, R² is -CO-, and n is 2.

5 A second preferred subclass pertains to compounds of the formula:

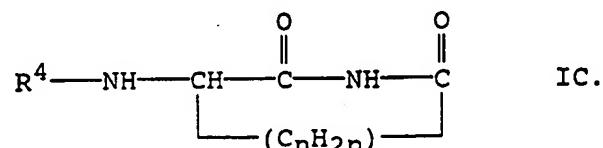


15 in which R³ is (i) phenyl substituted with nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, (ii) pyridyl, (iii) pyrrolyl, (iv) imidazolyl, (v) naphthyl, (vi) thienyl, (vii) quinolyl, (viii) furyl, or (ix) indolyl; 20 and

n has a value of 1, 2, or 3.

Preferred compounds of Formula IB are those wherein R³ is trifluoromethylphenyl, cyanophenyl, methoxyphenyl, fluorophenyl, or furyl, and n is 2.

25 A third preferred subclass pertains to compounds of the formula:

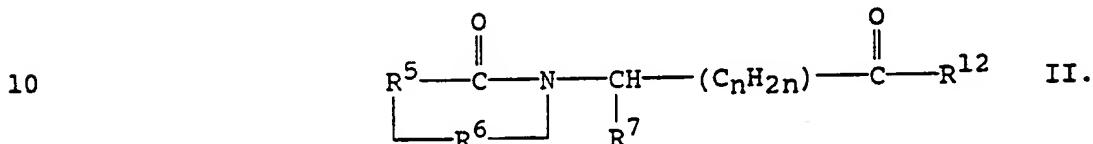


in which R⁴ is alanyl, arginyl, glycyl, phenylglycyl, histidyl, leucyl, isoleucyl, lysyl, methionyl, prolyl, sarcosyl, seryl, homoseryl, threonyl, thronyl, tyrosyl, valyl, 35

benzimidol-2-yl, benzoxazol-2-yl, phenylsulfonyl, methylphenylsulfonyl, or phenylcarbamoyl, and n has a value of 1, 2, or 3.

Preferred compounds of Formula IC are those wherein R⁴ is phenylsulfonyl or 2-amino-3-phenylpropanoyl and n is 2.

A second aspect of the present invention pertains to compounds of the formula:



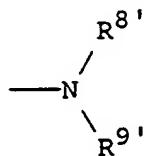
in which R⁵ is (i) o-phenylene, unsubstituted or substituted with 1 to 3 substituents each selected independently from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, or (ii) the divalent residue of pyridine, pyrrolidine, imidazole, naphthalene, or thiophene, wherein the divalent bonds are on vicinal ring carbon atoms;

R⁶ is -CO-, -CH₂-, or -SO₂-;

25 R⁷ is (i) hydrogen if R⁶ is -SO₂-, (ii) straight, branched, or cyclic alkyl of 1 to 12 carbon atoms, (iii) pyridyl, (iv) phenyl or phenyl substituted with one or more substituents each selected independently of the other from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo, (v) alkyl of 1 to 4 carbon atoms, (vi) benzyl unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon

atoms, alkoxy of 1 to 4 carbon atoms, or halo, (vii) naphthyl; (viii) benzyloxy, or (ix) imidazol-4-ylmethyl;

R^{12} is -OH, alkoxy of 1 to 12 carbon atoms, or

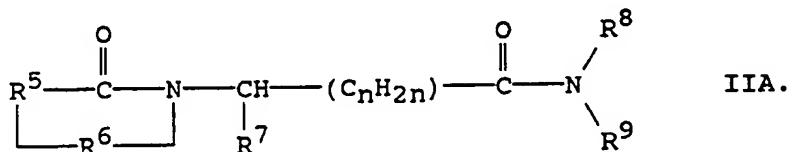


10 n has a value of 0, 1, 2, or 3;

$R^{8'}$ is hydrogen or alkyl of 1 to 4 carbon atoms; and

$R^{9'}$ is hydrogen, alkyl of 1 to 4 carbon atoms, $-COR^{10}$, or $-SO_2R^{10}$ in which R^{10} is hydrogen, alkyl of 1 to 4 carbon atoms, or phenyl.

15 A first preferred subclass of Formula II pertains to compounds of the formula:



25 in which R^5 is (i) o-phenylene, unsubstituted or substituted with 1 to 3 substituents each selected independently from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, or (ii) the divalent residue of pyridine, pyrrolidine, imidazole, naphthalene, or thiophene, wherein the 30 divalent bonds are on vicinal ring carbon atoms;

R^6 is $-CO-$, $-CH_2-$, or $-SO_2-$;

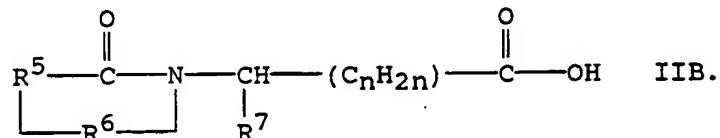
R^7 is (i) hydrogen if R^6 is $-SO_2-$, (ii) straight, branched, or cyclic alkyl of 1 to 12 carbon atoms, (iii) pyridyl, (iv) phenyl or phenyl substituted with one or more

substituents each selected independently of the other from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo, (v) alkyl of 1 to 4 carbon atoms, (vi) benzyl unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, (vii) napthyl, (viii) benzyloxy, or (ix) imidazol-4-ylmethyl;

n has a value of 0, 1, 2, or 3; R⁸ is hydrogen or alkyl of 1 to 4 carbon atoms; and R⁹ is hydrogen, alkyl of 1 to 4 carbon atoms, -COR¹⁰, or -SO₂R¹⁰ in which R¹⁰ is hydrogen, alkyl of 1 to 4 carbon atoms, or phenyl.

Preferred compounds of Formula IIA are those in which R⁵ is o-phenylene, R⁶ is -CO-; R⁷ is phenyl, substituted phenyl or pyridyl; n is 0 or 1, and each of R⁸ and R⁹ is hydrogen.

A second preferred subclass of Formula II pertains to compounds of the formula:



25

in which R⁵ is (i) o-phenylene, unsubstituted or substituted with 1 to 3 substituents each selected independently from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, or (ii) the divalent residue of pyridine, pyrrolidine, imidazole, naphthalene, or thiophene, wherein the divalent bonds are on vicinal ring carbon atoms;

35

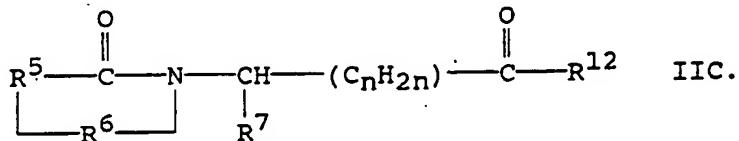
R⁶ is -CO-, -CH₂-, or -SO₂-;

R⁷ is (i) hydrogen if R⁶ is -SO₂-, (ii) straight, branched, or cyclic alkyl of 1 to 12 carbon atoms, (iii) pyridyl, (iv) phenyl or phenyl substituted with one or more substituents each selected independently of the other from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo, (v) alkyl of 1 to 4 carbon atoms, (vi) benzyl unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, (vii) napthyl, (viii) benzyloxy, or (ix) imidazol-4-ylmethyl; and

n has a value of 0, 1, 2, or 3.

Preferred compounds of Formula IIB are those in which R⁵ is o-phenylene, R⁶ is -CO-; R⁷ is phenyl, substituted phenyl or pyridyl; and n is 0 or 1.

A third preferred subclass of Formula II pertains to compounds of the formula:



25

in which R⁵ is (i) o-phenylene, unsubstituted or substituted with 1 to 3 substituents each selected independently from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, or (ii) the divalent residue of pyridine, pyrrolidine, imidizole, naphthalene, or thiophene, wherein the divalent bonds are on vicinal ring carbon atoms;

35

R⁶ is -CO-, -CH₂-, or -SO₂-;

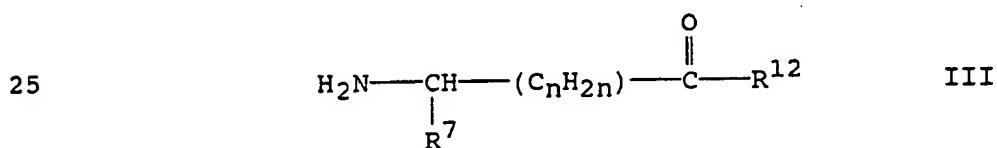
R⁷ is (i) hydrogen if R⁶ is -SO₂-, (ii) straight, branched, or cyclic alkyl of 1 to 12 carbon atoms, (iii) pyridyl, (iv) phenyl or phenyl substituted with one or more substituents each selected independently of the other from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo, (v) alkyl of 1 to 4 carbon atoms, (vi) benzyl unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, (vii) naphthyl, (viii) benzyloxy, or (ix) imidazol-4-ylmethyl;

R¹² is -OH or alkoxy of 1 to 12 carbon atoms; and

n has a value of 0, 1, 2, or 3.

Preferred compounds of Formula IIC are those in which R⁵ is o-phenylene or amino substituted o-phenylene; R⁶ is -CO-; R⁷ is phenyl, substituted phenyl or pyridyl; R¹² is methoxy; and n is 0 or 1.

A third aspect of the present invention pertains to compounds of the formula:

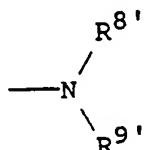


in which

R⁷ is (i) straight, branched, or cyclic alkyl of 1 to 12 carbon atoms, (ii) pyridyl, (iii) phenyl or phenyl substituted with one or more substituents each selected independently of the other from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy,

5 acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo, (iv) benzyl unsubstituted or substituted with one to three substituents selected from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, (v) napthyl, (vi) benzyloxy, or (vii) imidazol-4-ylmethyl;

10 R¹² is -OH, alkoxy of 1 to 12 carbon atoms, -O-CH₂-pyridyl,
-O-benzyl, or



15

where n has a value of 0, 1, 2, or 3;

R^8' is hydrogen or alkyl of 1 to 10 carbon atoms; and

20 R⁹ is hydrogen, alkyl of 1 to 10 carbon atoms, -CH₂-pyridyl, benzyl, -COR¹⁰, or -SO₂R¹⁰ in which R¹⁰ is hydrogen, alkyl of 1 to 4 carbon atoms, or phenyl.

Typical compounds of this invention include 2-(2,6-dioxo-3-piperidinyl)-4-azaisoindoline-1,3-dione; 2-(2,6-dioxo-3-piperidinyl)-benzo[e]isoindoline-1,3-dione; 5-(2,6-dioxo-3-piperidinyl)-pyrrolo[3,4-d]imidazole-4,6-dione; 3-(trifluoromethylphenylcarboxamido) piperidine-2,6-dione; 3-(cyano-phenylcarboxamido)piperidine-2,6-dione; 3-(methoxyphenylcarboxamido)- piperidine-2,6-dione; 3-(3-pyridylcarboxamido)-piperidine-2,6-dione; 3-(2-furylcarboxamido)piperidine-2,6-dione; 3-phenylsulfonamidopiperidine-2,6-dione; 3-(2-amino-3-phenylpropaneamido)-piperidine-2,6-dione; 2-phthalimido-2-phenylacetamide; 3-phthalimido-3-phenylpropanamide; 2-phthalimido-3-phenylpropanamide; 2-phthalimido-3-(4-hydroxy)phenylpropanamide; 3-phthalimido-3-phenylpropionic acid; 2-phthalimido-2-(4-hydroxyphenyl)acetic acid; 2-phthalimido-2-phenyl-

acetic acid; 2-phthalimido-2-(4-fluorophenyl)acetic acid; 2-phthalimido-2-(2-fluorophenyl)acetic acid; 2-phthalimido-2-(4-fluorophenyl)acetamide; 2-phthalimido-3-phenylpropionic acid; 2-phthalimido-4-methylpentanoic acid; 3-phenylcarboxamido-piperidine-2,6-dione; 2-phthalimidoacetamide; 3-phthalimido-propanamide; 3-phthalimidoimidazoline-2,5-dione; 3-phenylcarboxamidopropanamide; 2-phthalimido-3-carbamoylpropionic acid; 2-(1,3-dioxo-4-azaisoindolinyl)-3-carbamoylpropionic acid; 3-(1,3-dioxo-4-azaisoindolinyl)piperidine-2,6-dione; 2-(1,3-dioxo-4-azaisoindolinyl)-acetamide; 3-phthalimido-3-carbamoyl-propionic acid; 4-phthalimidobutyramide; 4-phthalimidobutyric acid; methyl 3-phthalimido-3-(4-methoxyphenyl)propionate; ethyl 3-phthalimido-3-(4-methoxyphenyl)propionate; methyl 3-phthalimido-3-phenylpropionate; and propyl 3-phthalimido-3-(4-methoxyphenyl)propionate; 2-(1'-Oxo-isoindoline)-2-phenylethanoic acid; 2-(1'-Oxo-isoindoline)-2-phenylacetamide; 3-Phenyl-2-(1'-oxo-isoindoline)propanoic acid; 3-Phenyl-2-(1'-oxo-isoindoline)propionamide; 3-Phenyl-3-(1'-oxo-isoindoline)propanoic acid; 3-Phenyl-3-(1'-oxo-isoindoline)propanamide; 3-(4'-Methoxyphenyl)-3-(1'-oxo-isoindoline)propanoic acid; 3-(4'-Methoxyphenyl)-3-(1'-oxo-isoindoline)propionamide; 3-(3',4'-Dimethoxyphenyl)-3-(1'-oxo-isoindoline)propanoic acid; 3-(3',4'-Dimethoxyphenyl)-3-(1'-oxo-isoindoline)propionamide; 3-(3',4'-Diethoxyphenyl)-3-(1'-oxo-isoindoline)propionic acid; 3-(3',4'-Diethoxyphenyl)-3-phthalimidopropionamide; 3-Phthalimido-3-(4'-propoxyphenyl)propionic acid; 3-Phthalimido-3-(4'-propoxyphenyl)propionamide; Ethyl 3-Amino-3-(3'-pyridyl)propionate hydrochloride; Ethyl 3-phthalimido-3-(3'-pyridyl)propionate; 3-Phthalimido-3-(3',4'-dimethoxyphenyl)propionic acid; 3-Phthalimido-3-(3',4'-dimethoxyphenyl)propionamide; Ethyl 3-Amino-3-(3',4'-dimethoxyphenyl)propionate; Ethyl 3-phthalimido-3-(3',4'-dimethoxyphenyl)propionate; 3-Phthalimido-3-(3',4'-dimethoxyphenyl)propionic amylamide; 3-Phthalimido-3-(3',4'-dimethoxyphenyl)propionic benzylamide; 3-Phthalimido-3-(3',4'-dimethoxyphenyl)propionic ethylamide; 3-Phthalimido-3-(4'-ethoxyphenyl)propionic acid; 3-phthalimido-3-(4'-ethoxyphenyl)propionamide; 3-(cis-hexahydrophthalimido)-3-phenylpropionic acid; 3-(cis-hexahydrophthalimido)-3-phenylpropionamide; 3-(4-methylphthalimido)-3-phenylpropionic acid; 3-(Cis-

5-norbonene-endo-2,3-dicarboxylic imide)-3-phenylpropionic acid; 3-(2,3,4,5-Tetrachlorophthalimido)-3-(4'-methoxyphenyl)-propionic acid; 3-(4'-nitrophthalimido)-3-(4'-methoxyphenyl)-propionic acid; 3-Phthalimido-3-(2'-naphthyl)propionic acid; 3-Phthalimido-3-(2'-naphthyl)propionamide; Methyl 3-(1,3-dioxo-5-azaisoindol-2-yl)-3-(3',4'-dimethoxyphenyl)-propionate; 3-Phthalimido-3-(4'-benzyloxy-3'-methoxyphenyl)propionic acid; 3-Phthalimido-3-(4'-benzyloxy-3'-methoxyphenyl)propionamide; 3-phthalimido-3-(4'-butoxy-3'-methoxyphenyl)propionic acid; 3-phthalimido-3-(4'-butoxy-3'-methoxyphenyl)propionamide; 2-(3,4,5,6-Tetrachlorophthalimido)-2-phenylacetic acid; 2-(4',5'-dichlorophthalimido)-2-phenylacetic acid; 2-phenyl-2-(3'-nitrophthalimido)acetic acid; 3-(4'-methoxyphenyl)-3-(3'-nitrophthalimido)propionic acid; 3-(4',5'-dichlorophthalimido)-3-(4'-methoxyphenyl)propionic acid; 3-Pyridinemethyl 3-phthalimido-3-(3',4'-dimethoxyphenyl)propionate; N-3-Methyl-pyridyl 3-phthalimido-3-(3',4'-dimethoxyphenyl)propionamide; 3-Phthalimido-3-(3',4'-dichlorophenyl)propionamide; Methyl 3-amino-3-(3',4'-dimethoxyphenyl)propionate hydrochloride; 20 Methyl 3-phthalimido-3-(3',4'-dimethoxyphenyl)propionate; Methyl (S)-N-Benzyl-N-(R)-a-methylbenzyl-3-(3',4'-dimethoxyphenyl)propionate; Methyl (S)-3-amino-3-(3',4'-dimethoxyphenyl)propionate hydrochloride; Methyl (S)-3-phthalimido-3-(3',4'-dimethoxyphenyl)propionate; Methyl (R)-3-(N-benzyl-N-(S)-a-methylbenzylamino)-3-(3',4'-dimethoxyphenyl)propionate; Methyl (R)-3-amino-3-(3',4'-dimethoxyphenyl)propionate hydrochloride; methyl (3R)-3-phthalimido-3-(3',4'-dimethoxyphenyl)-propionate.

30 The term alkyl as used herein denotes a univalent saturated branched or straight hydrocarbon chain. Unless otherwise stated, such chains can contain from 1 to 18 carbon atoms. Representative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl, isohexyl, heptyl, 35 octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, and the like. When qualified by "lower", the alkyl group will contain from 1

to 6 carbon atoms. The same carbon content applies to the parent term "alkane" and to derivative terms such as "alkoxy".

5 The compounds can be used, under the supervision of qualified professionals, to inhibit the undesirable effects of TNF α . The compounds can be administered orally, rectally, or parenterally, alone or in combination with other therapeutic agents including antibiotics, steroids, etc., to a mammal in need of treatment. Oral dosage forms include tablets, capsules, dragees, and similar shaped, compressed pharmaceutical forms. Isotonic saline solutions containing 20-100 mg/mL can be used for parenteral administration which includes intramuscular, intrathecal, intravenous and intra-arterial routes of administration. Rectal administration can be effected through the use of suppositories formulated from conventional carriers 10 such as cocoa butter.

15

Dosage regimens must be titrated to the particular indication, the age, weight, and general physical condition of the patient, and the response desired but generally doses will be from about 10 to about 500 mg/day as needed in single or multiple daily administration. In general, an initial treatment regimen can be copied from that known to be effective in interfering with TNF α activity for other TNF α mediated disease states by the compounds of the present invention. Treated individuals will be regularly checked for T cell numbers and T4/T8 ratios and/or measures of viremia such as levels of reverse transcriptase or viral proteins, and/or for progression of cytokine-mediated disease associated problems such as cachexia or muscle degeneration. If no effect is soon following the normal treatment regimen, then the amount of cytokine activity interfering agent administered is increased, e.g., by 20 fifty percent a week.

25

30

The compounds of the present invention also can be used topically in the treatment or prophylaxis of topical disease states mediated or exacerbated by excessive TNF α production,

respectively, such as viral infections, such as those caused by the herpes viruses, or viral conjunctivitis, etc.

5 The compounds also can be used in the veterinary treatment of mammals other than humans in need of prevention or inhibition of TNF_α production. TNF_α mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples include feline immunodeficiency virus, equine infectious anaemia virus, caprine 10 arthritis virus, visna virus, and maedi virus, as well as other lentiviruses.

15 Certain of these compounds possess centers of chirality and can exist as optical isomers. Both the racemates of these isomers and the individual isomers themselves, as well as diastereomers when there are two chiral centers, are within the scope of the present invention. The racemates can be used as such or can be separated into their individual isomers mechanically as by chromatography using a chiral absorbant. 20 Alternatively, the individual isomers can be prepared in chiral form or separated chemically from a mixture by forming salts with a chiral acid, such as the individual enantiomers of 10-camphorsulfonic acid, camphoric acid, alpha-bromocamphoric acid, methoxyacetic acid, tartaric acid, diacetyltar- 25 taric acid, malic acid, pyrrolidone-5-carboxylic acid, and the like, and then freeing one or both of the resolved bases, optionally repeating the process, so as obtain either or both substantially free of the other; i.e., in a form having an optical purity of >95%.

30 The compounds can be prepared using methods which are known in general for the preparation of imides. However, the present invention also pertains to an improvement in the formation of the final compounds, as discussed below in greater detail.

An N-alkoxycarbonylimide and an amine thus are allowed to react in the presence of a base such as sodium carbonate or sodium bicarbonate substantially as described by Shealy et al., Chem. & Ind., (1965) 1030-1031) and Shealy et al., J. Pharm. Sci. 57, 757-764 (1968) to yield the N-substituted imide. Alternatively, a cyclic acid anhydride can be reacted with an appropriate amine to form an imide. Formation of a cyclic imide also can be accomplished by refluxing a solution of an appropriately substituted dicarboxylic acid monoamide in anhydrous tetrahydrofuran with N,N'-carbonyldiimidazole. In contrast to prior art methods which produced a yield of less than 50%, this reaction produces yields in excess of 60%, in some cases greater than 90%. This reaction also has broader applicability, being useful not only in the preparation of compounds of the present invention but also in the preparation of known compounds such as thalidomide.

Prevention or inhibition of production of TNF α by these compounds can be conveniently assayed using anti-TNF α antibodies. For example, plates (Nunc Immunoplates, Roskilde, DK) are treated with 5 μ g/mL of purified rabbit anti-TNF α antibodies at 4°C for 12 to 14 hours. The plates then are blocked for 2 hours at 25°C with PBS/0.05% Tween containing 5 mg/mL BSA. After washing, 100 μ L of unknowns as well as controls are applied and the plates incubated at 4°C for 12 to 14 hours. The plates are washed and assayed with a conjugate of peroxidase (horseradish) and mouse anti-TNF α monoclonal antibodies, and the color developed with o-phenylenediamine in phosphate-citrate buffer containing 0.012% hydrogen peroxide and read at 492 nm.

The following examples will serve to further typify the nature of this invention but should not be construed as a limitation in the scope thereof, which scope is defined solely by the appended claims.

EXAMPLE 1

5 A stirred suspension of (S)-glutamine (14.6 g, 100 mmol) and 2,3-pyridinedicarboxylic anhydride (14.9 g, 100 mmol) in 100 mL of acetic acid is heated and refluxed for 1 hour. The reaction solution is cooled to form a solid. The solid is removed by filtration and washed with acetic acid to yield 7.11 g (26%) of 2-(1,3-dioxo-4-azaisoindolin-2-yl)glutaramic acid. The product can be further purified by slurring in 700 mL of refluxing ethanol, cooling, filtering, and drying to 10 produce a white powder with a melting point of 222-226°C; ¹H NMR (DMSO-d₆) δ 13.25 (br s, 1 H, COOH), 9.04 (dd, 1 H, J = 1.2, 4.9 Hz, pyr), 8.37 (dd, 1 H, J = 1.2, 7.8 Hz, pyr), 7.85 (dd, 1 H, J = 4.9, 7.8 Hz, pyr), 7.20 (s, 1 H, CONH₂), 6.73 (s, 1 H, CONH₂), 4.83 (dd, 1 H, J = 10.2, 4.8 Hz, CHN), 2.55-15 1.90 (m, 4 H, CH₂CH₂); ¹³C NMR (DMSO-d₆) δ 1173.22, 170.21, 165.8, 165.7, 155.4, 150.9, 131.7, 128.3, 126.9, 51.5, 31.4, 24.0.

Utilization of asparagine in place of glutamine produces 2-(1,3-dioxo-4-azaisoindolin-2-yl)-malonamic acid.

20 By substituting equivalent amounts of 2,3-naphthalenedicarboxylic anhydride and 4,5-imidazoledicarboxylic anhydride for 2,3-pyridinedicarboxylic anhydride in the foregoing procedure, there are respectively obtained 2-(1,3-dioxobenzo[e]isoindolin-2-yl)glutaramic acid and 2-(4,6-dioxo-25 pyrrolo[3,4-d]imidazol-5-yl)glutaramic acid.

EXAMPLE 2

30 A stirred suspension of 1.39 g, 5.01 mmol, of 2-(1,3-dioxo-4-azaisoindolin-2-yl)glutaramic acid (see Example 1), N,N'-carbonyldiimidazole (0.890 g, 5.49 mmol) and N,N-dimethylaminopyridine (0.005 g, 0.04 mmol) in 20 mL of tetrahydrofuran is refluxed for 15 hours. The reaction slurry is cooled and the solid removed by filtration and washed with minimal tetrahydrofuran. 2-(2,6-Dioxo-3-piperidinyl)-4-aza-

isoindoline-1,3-dione (0.859 g, 66%) is recovered as a white powder. ^1H NMR (DMSO-d₆) δ 11.18 (s, 1 H, NHCO), 9.04 (d, 1 H, J = 5.0 Hz, pyr), 8.39 (d, 1 H, J = 7.7 Hz, pyr), 7.86 (dd, 1 H, J = 5.0, 7.7 Hz, pyr), 5.25 (dd, 1 H, J = 15.3, 13 Hz, 1 H, CHCO), 3.05-2.75 (m, 1 H, CH₂CO), 2.75 (m, 2 H, CH₂CO, CH₂), 2.20-2.00 (m, 1 H, CH₂CO, CH₂); ^{13}C NMR (DMSO-d₆) δ 172.6, 169.6, 165.4, 155.3, 150.8, 131.7, 128.2, 126.9, 49.0, 30.8, 21.8. Anal. Calcd for C₁₂H₉N₃O₄. Theory 55.60, 3.50, 16.21. Found 55.50, 3.53, 16.11.

10 Substitution of 2-(1,3-dioxo-4-azaisoindolin-2-yl)malo-namic acid in the foregoing procedure yields 2-(2,5-dioxo-3-pyrrolidinyl)-4-azaisoindoline-1,3-dione.

15 By substituting equivalent amounts of 2-(1,3-dioxobenzo[e]isoindolin-2-yl)glutaramic acid and 2-(4,6-dioxo-pyrrolo[3,4-d]imidazol-5-yl)glutaramic acid in the foregoing procedure, there are respectively obtained 2-(2,6-dioxo-3-piperidinyl)-benzo[e]isoindoline-1,3-dione and 5-(2,6-dioxo-3-piperidinyl)-pyrrolo[3,4-d]imidazole-4,6-dione.

EXAMPLE 3

20 A solution of L-glutamine (2.92 g, 20.0 mmol) and sodium hydroxide (20 mmol) in water is added to a stirred solution of phenylisocyanate (2.4 g, 2.2 mL, 20 mmol) in acetonitrile (40 mL). The reaction mixture is stirred for 45 hours and is partially concentrated to remove acetonitrile. The reaction mixture is washed with ethyl acetate (2 x 25 mL each). The pH of the reaction mixture is adjusted to 1 - 2 with 4N hydrochloric acid. The slurry of the reaction mixture is filtered and the solid washed and dried to yield 4.70 g of N-phenyl-N'-(4-carboxybutyramide)urea (89%) as a white powder.

30 By substituting 4-trifluoromethylphenylisocyanate, 3-cyanophenylisocyanate, 2-methoxyphenylisocyanate, fur-2-ylisocyanate, and pyrid-3-ylisocyanate for phenylisocyanate in the foregoing procedure, there are respectively obtained N-(4-tri-

fluoromethylphenyl)-N'-(4-carboxybutyramide)urea, N-(3-cyanophenyl)-N'-(4-carboxybutyramide)urea, N-(2-methoxyphenyl)-N'-(4-carboxybutyramide)urea, N-(fur-2-yl)-N'-(4-carboxybutyramide)urea, and N-(pyrid-3-yl)-N'-(4-carboxybutyramide)urea.

5

EXAMPLE 4

N-Phenyl-N'-(4-carboxybutyramide)urea (2.00 g, 7.54 mmol) is mixed with carbonyldiimidazole (1.24 g, 7.95 mmol) in tetrahydrofuran (30 mL) is heated and refluxed for 16 hours. 10 The reaction mixture is concentrated and the residue slurried in water (25 mL). The resulting slurry is filtered and the solid is washed with water and air dried to yield 0.63 g of 3-phenylcarboxamidopiperidine-2,6-dione which can be alternatively named as N-phenyl-N'-(2-glutarimide)urea as a white 15 flocculent powder. After being allowed to stand, the filtrate is refiltered to yield 0.70 g of additional material. ^1H NMR (DMSO-d₆) δ 8.51 (s, 1H, CONHCO), 7.6-7.2 (m, 6 H, Ar, ArNH), 6.83 (s, 1 H, NHCH), 4.26 (t, 1H, CHCO), 2.4-1.8 (m, 4 H, CH₂CH₂); ^{13}C NMR (DMSO-d₆) δ 173.2, 155.6, 132.2, 128.7, 20 127.7, 126.7, 55.7, 29.8, 27.2. Anal. Calcd for C₁₂H₁₃N₃O₃. Theoretical: C, 58.29; H, 5.29; N, 16.99. Found: C, 58.12; H, 5.17; N, 17.02.

By substituting N-(4-trifluoromethylphenyl)-N'-(4-carboxybutyramide)urea, N-(3-cyanophenyl)-N'-(4-carboxybutyramide)urea, N-(2-methoxyphenyl)-N'-(4-carboxybutyramide)urea, N-(fur-2-yl)-N'-(4-carboxybutyramide)urea, and N-(pyrid-3-yl)-N'-(4-carboxybutyramide)urea for N-phenyl-N'-(4-carboxybutyramide)urea in the foregoing procedure, there are respectively obtained 3-(4-trifluoromethylphenylcarboxamido)piperidine-2,6-dione, 3-(3-cyanophenylcarboxamido)piperidine-2,6-dione, 3-(2-methoxyphenylcarboxamido)piperidine-2,6-dione, 3-(fur-2-ylcarboxamido)piperidine-2,6-dione, and 3-(pyrid-3-ylcarboxamido)piperidine-2,6-dione.

EXAMPLE 5

To a stirred mixture of phenylglycine (3.0 g, 20 mmol) and sodium carbonate (2.23 g, 21 mmol) in 450 mL of water is added N-carbethoxyphthalimide (4.38 g, 20 mmol). After 45 minutes, the reaction slurry is filtered. The filtrate is stirred and the pH adjusted to 1-2 with 4 N hydrochloric acid. After 1 hour, the resulting slurry is filtered and the solid washed with water. The solid is dried in vacuo (60°C, <1mm) to afford 2.88 g (51%) of 2-phthalimido-2-phenylacetic acid, which can be alternatively named as N-phthaloylphenylglycine, as a white powder.

Use of β -phenyl- β -alanine, α -phenyl- β -alanine, histidine, and tyrosine in place of phenylglycine in the procedure of this example yields respectively 3-phthalimido-3-phenylpropionic acid, 2-phthalimido-3-phenylpropionic acid, 2-phthalimido-3-imidazolylpropionic acid, and 2-phthalimido-3-(4-hydroxyphenyl)propionic acid.

EXAMPLE 6

To a stirred mixture of 2-phthalimido-2-phenylacetic acid (2.50 g, 8.89 mmol) in tetrahydrofuran (50 mL) is added carbonyldiimidazole (1.50 g, 9.25 mmol) and a few crystals of 4-dimethylaminopyridine. The reaction is then heated to 50°C for 45 minutes. After the reaction mixture cools to room temperature, 1 mL of concentrated ammonium hydroxide is added via syringe. The reaction is stirred for 1 hour, then diluted with 50 mL of water and partially concentrated to remove the majority of the tetrahydrofuran. The resulting slurry is filtered and the solid washed with copious amounts of water. The solid is dried in vacuo (60°C, <1mm) to afford 1.9 g (76%) of 2-phthalimido-2-phenylacetamide, which may be alternatively named as N-phthaloylphenylglycinamide, as an off-white powder: mp 218-220°C; ^1H NMR (DMSO-d₆) δ 9.00-7.75 (m, 4 H, Ar), 7.61 (br s, 1 H, CONH₂), 7.55-7.20 (m, 6 H, Ar, CONH₂), 5.82 (s, 1 H, CHCO₂); ^{13}C NMR (DMSO-d₆) δ 168.2, 167.1, 135.6, 134.5,

131.4, 129.4, 127.9, 127.7, 123.1, 56.3. Anal (C₁₆H₁₂N₂O₃),
C, H, N.

Use of 3-phthalimido-3-phenylpropionic acid, 2-phthalimido-3-phenylpropionic acid, 2-phthalimido-3-imidazolylpropionic acid, and 2-phthalimido-3-(4-hydroxyphenyl)propionic acid in place of 2-phthalimido-2-phenylacetic acid in the procedure of this example yields respectively 3-phthalimido-3-phenylpropanamide, 2-phthalimido-3-phenylpropanamide, 2-phthalimido-3-imidazolylpropanamide, and 2-phthalimido-3-(4-hydroxy)phenylpropanamide.

EXAMPLE 7

To a stirred mixture of β -alanine (4.45 g, 50.0 mmol) and sodium carbonate (5.35 g, 50.5 mmol) in 100 mL of water is added N-carbethoxyphthalimide (10.95 g, 50.0 mmol). After 1.5 hour, the reaction slurry is filtered. The filtrate is stirred and the pH adjusted to 1-2 with 4 N hydrochloric acid. After 15 minutes, the resulting slurry is filtered and the solid washed with water. The solid is dried in vacuo (60°C, <1mm) to afford 6.96 g (64%) of N-phthaloyl- β -alanine, which can be alternatively named as 3-phthalimidopropionic acid, as a white powder.

EXAMPLE 8

To a stirred solution of N-phthaloyl- β -alanine (2.19 g, 10.0 mmol) in tetrahydrofuran (25 mL) is added carbonyldimidazole (1.62 g, 10.0 mmol) and a few crystals of 4-N,N-dimethylaminopyridine followed by 15 mL of tetrahydrofuran. The reaction is then heated to 40-45°C for 1 hour. After the reaction mixture cools to room temperature, 1 mL of concentrated ammonium hydroxide is added via syringe. The reaction is stirred for 20 minutes and the resulting slurry filtered and the solid washed with tetrahydrofuran. The solid is dried in vacuo (60°C, <1mm) to afford 1.72 g (79%) of N-phthaloyl- β -alanine amide, which can be alternatively named as

3-phthalimidopropanamide, as a white powder: mp 252-253°C; ^1H NMR (DMSO-d₆) δ 8.00-7.70 (m, 4 H, Ar), 7.45 (br s, 1 H, CONH₂), 6.89 (br s, 1 H, CONH₂), 3.78 (t, 2 H, J = 7 Hz, CH₂CO), 2.43 (t, 2 H, CH₂); ^{13}C NMR (DMSO-d₆) δ 171.5, 167.6, 134.2, 131.6, 122.9, 34.1, 33.5. Anal. Calcd for C₁₁H₁₀N₂O₃. Theoretical: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.49; H, 4.59; N, 12.82.

EXAMPLE 9

To a stirred solution of glycinate hydrochloride (2.20 g, 20.0 mmol) and sodium carbonate (2.54 g, 24 mmol) in 25 mL of water is added N-carbethoxyphthalimide (4.38 g, 20.0 mmol). The resulting suspension is stirred for 1.5 hour and then filtered to afford 3.22 g (79%) of the crude product as a white powder. The crude product is slurried in 200 mL of refluxing ethanol. The resulting suspension after cooling to room temperature is filtered and the solid dried in vacuo (60°C, <1mm) to afford 2.65 g (65%) of N-phthaloylglycinate as a white powder: mp 199-201°C; ^1H NMR (DMSO-d₆) δ 8.00-7.8 (m, 4 H, Ar), 7.70 (br s, 1 H, CONH₂), 7.26 (br s, 1 H, CONH₂), 4.16 (s, 2 H, CH₂); ^{13}C NMR (DMSO-d₆) δ 167.8, 167.5, 134.4, 131.7, 123.1, 39.9. Anal. Calcd for C₁₁H₁₀N₂O₃. Theoretical: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.49; H, 4.59; N, 12.82.

EXAMPLE 10

To a stirred solution of L-glutamine (43.8 g, 300 mmol) and sodium carbonate (33.4 g, 315 mmol) in 750 mL of water is rapidly added N-carbethoxyphthalimide [65.8 (97% pure, 67.8 g), 300 mmol] as a solid. After 1 hour, the reaction mixture is filtered to remove unreacted N-carbethoxyphthalimide. The pH of the stirred filtrate is adjusted to 3-4 with 4N hydrochloric acid. The mixture is then seeded with N-phthaloyl-L-glutamine and the pH adjusted to 1-2 with 4 N hydrochloric acid. The resulting slurry is stirred for 1 hour. The slurry is filtered and the solid washed with copious amounts of water. The solid is air-dried and then dried in

vacuo (60°C , $<1\text{mm}$) overnight to afford 49.07 g (59%) of N-phthaloyl-L-glutamine, which can be alternatively named as 2-phthalimidoglutaramic acid, as a white powder.

EXAMPLE 11

5 A stirred mixture of N-phthaloyl-L-glutamine (48.0 g, 174 mmol), carbonyldiimidazole (30.43 g, 188 mmol), and 4-dimethylaminopyridine (0.105 g, 0.861 mmol) in anhydrous tetrahydrofuran (300 mL) is heated to reflux for 16 hours. The reaction slurry is filtered and the solid washed with 10 methylene chloride (200 mL). The solid is air-dried and then dried in vacuo (60°C , $<1\text{mm}$) to afford 40.40 g (90%) of thalidomide as a white powder. ^1H NMR (DMSO-d₆) δ 11.16 (s, 1 H, NH), 8.05-7.80 (br s, 4 H, Ar), 5.18 (dd, 1 H, J = 12, 5 Hz, CHCO), 3.05-2.85 (m, 1 H, CH₂CO), 2.70-2.45 (m, 2 H, CH₂CH₂), 2.15-2.00 (M, 1 H, CH₂). ^{13}C NMR (DMSO-d₆) δ 172.8, 15 169.8, 167.1, 134.9, 131.2, 123.4, 49.0, 30.9, 22.0.

EXAMPLE 12

20 A stirred suspension of (S)-glutamine (14.6 g, 100 mL) and pyridine-2,3-dicarboxylic anhydride (14.9 g, 100 mmol) in 100 mL of acetic acid is heated at reflux for 1 hour. The resulting solution is allowed to cool. The solid which forms upon cooling is filtered and the solid washed with acetic acid and dried to afford 7.11 g (26%) of crude product. The crude product is slurried in 700 mL of refluxing ethanol, the suspension cooled, and the slurry collected by filtration and dried to afford 6.10 g (23%) of N-quinolinylglutamine, which 25 can be alternatively named as 2-(1,3-dioxo-4-azaisoindol-2-yl)-3-carbamoylpropionic acid, as a white powder. mp 222-226°C; ^1H NMR (DMSO-d₆) δ 13.25 (br s, 1 H, COOH), 9.04 (dd, 1 H, J = 1.2, 4.9 Hz, pyr), 8.37 (dd, 1 H, J = 1.2, 7.8 Hz, pyr), 7.85 (dd, 1 H, J = 4.9, 7.8 Hz, pyr), 7.20 (s, 1 H, CONH₂), 6.73 (s, 1 H, CONH₂), 4.83 (dd, 1 H, J = 10.2, 4.8 Hz, CHN), 2.55-1.90 (m, 4 H, CH₂CH₂); ^{13}C NMR (DMSO-d₆) δ 1173.22,

170.21, 165.8, 165.7, 155.4, 150.9, 131.7, 128.3, 126.9, 51.5,
31.4, 24.0.

EXAMPLE 13

A stirred suspension of N-quinolinylglutamine (1.39 g, 5.01 mmol), carbonyldiimidazole (0.890 g, 5.49 mmol), and N,N-dimethylpyridine (0.005 g, 0.04 mmol) in 20 mL of tetrahydrofuran is heated at reflux for 15 hours. After cooling, the reaction slurry is filtered and the solid washed with minimal tetrahydrofuran to afford, after drying 0.859 g (66%) of N-quinolinylglutarimide, which can be, alternatively named as 3-(1,3-dioxo-4-azaisoindol-2-yl)-2,6-dioxopiperidine, as a white powder: ^1H NMR (DMSO-d₆) δ 11.18 (s, 1 H, NHCO), 9.04 (d, 1 H, J = 5.0 Hz, pyr), 8.39 (d, 1 H, J = 7.7 Hz, pyr), 7.86 (dd, 1 H, J = 5.0, 7.7 Hz, pyr), 5.25 (dd, 1 H, J = 15.3, 13 Hz, 1 H, CHCO), 3.05-2.75 (m, 1 H, CH₂CO), 2.75 (m, 2 H, CH₂CO, CH₂), 2.20-2.00 (m, 1 H, CH₂CO, CH₂); ^{13}C NMR (DMSO-d₆) δ 172.6, 169.6, 165.4, 155.3, 150.8, 131.7, 128.2, 126.9, 49.0, 30.8, 21.8. Anal. Calculated for C₁₂H₉N₃O₄. Theory 55.60, 3.50, 16.21. Found 55.50, 3.53, 16.11.

20

EXAMPLE 14

To a stirred mixture of phenylglycine (3.0 g, 20 mmol) and sodium carbonate (2.23 g, 21 mmol) in 450 mL of water is added N-carbethoxyphthalimide (4.38 g, 20 mmol). After 45 minutes, the reaction slurry is filtered. The filtrate is stirred and the pH adjusted to 1-2 with 4 N hydrochloric acid. After 1 hour, the resulting slurry is filtered and the solid washed with water. The solid is dried in vacuo (60°C, < 1mm) to afford 2.88 g (51%) of 2-phthalimido-phenylacetic acid as a white powder.

30

By employing (R)-phenylglycine, there is obtained (R)-2-phthalimido-phenylacetic acid, as a white powder: mp 175-177°C; ^1H NMR (DMSO-d₆, 250 MHz) δ 12.50 (br s, 1H), 7.95-7.85 (m, 4H), 7.55-7.28 (m, 5H), 6.04 (s, 1H); ^{13}C NMR (DMSO-

d₆) δ 168.9, 166.9, 135.0, 134.9, 131.0, 129.1, 128.1, 127.9, 123.5, 56.1. Anal. Calculated for C₁₆H₁₁NO₄. Theoretical: C, 68.32; H, 3.94; N, 4.98. Found: C, 68.32; H, 3.85; N, 4.95.

5 Likewise from (S)-phenylglycine, there is obtained (S)-2-phthalimido-phenylacetic acid as a white powder: mp 180-184°C; 1H NMR (DMSO-d₆, 250 MHz) δ 12.5 (br s, 1H), 7.95-7.85 (m, 4H), 7.55-7.28 (m, 5H), 6.04 (s, 1H); 13C NMR (DMSO-d₆) δ 168.9, 166.9, 135.0, 134.9, 130.9, 129.1, 128.1, 127.9, 123.5, 55.1. Anal. Calculated for C₁₆H₁₁NO₄. Theoretical: C, 68.32; H, 3.94; N, 4.98. Found: C, 68.14; H, 3.87; N, 4.96.

EXAMPLE 15

15 To a stirred solution of N-phthaloylglycine (2.50 g, 8.89 mmol) in tetrahydrofuran (50 mL) is added carbonyldiimidazole (1.50 g, 9.25 mmol) and a few crystals of 4-N,N-dimethyl-aminopyridine. The reaction is then heated to 50°C for 45 minutes. After the reaction mixture had cooled to room temperature, 1 mL of concentrated ammonium hydroxide is added via syringe. The reaction is stirred for 1 hour, then diluted with 50 mL of water and partially concentrated to remove the 20 majority of the tetrahydrofuran. The resulting slurry was filtered and the solid washed with copious amounts of water. The solid was dried in vacuo (60°C, < 1mm) to afford 1.9 g (76%) of 2-phthalimido-2-phenylacetamide as an off-white powder: mp 218-220°C; 1H NMR (DMSO-d₆) δ 9.00-7.75 (m, 4 H, Ar), 7.61 (br s, 1 H, CONH₂), 7.55-7.20 (m, 6 H, Ar, CONH₂), 5.82 (s, 1 H, CHCO₂); 13C NMR (DMSO-d₆) δ 168.2, 167.1, 135.6, 134.5, 131.4, 129.4, 127.9, 127.7, 123.1, 56.3.

EXAMPLE 16

30 To a stirred mixture of β -alanine (4.45 g, 50.0 mmol) and sodium carbonate (5.35 g, 50.5 mmol) in 100 mL of water is added N-carbethoxyphthalimide (10.95 g, 50.0 mmol). After 1.5 hour, the reaction slurry is filtered. The filtrate is stirred and the pH adjusted to 1-2 with 4 N hydrochloric acid.

After 15 minutes, the resulting slurry is filtered and the solid washed with water. The solid is dried in vacuo (60°C, < 1mm) to afford 6.96 g (64%) of N-phthaloyl- β -alanine, which can be alternatively named as 3-phthalimido-3-phenylpropionic acid, as a white powder.

5

EXAMPLE 17

To a stirred solution of N-phthaloyl- β -alanine (2.19 g, 10.0 mmol) in tetrahydrofuran (25 mL) is added carbonyldiimidazole (1.62 g, 10.0 mmol) and a few crystals of 4-N,N-dimethylaminopyridine, followed by 15 mL of tetrahydrofuran. The mixture is heated at 40-45°C for 1 hour. After the reaction mixture is cooled to room temperature, 1 mL of concentrated ammonium hydroxide is added via syringe. The reaction is stirred for 20 minutes and the resulting slurry is filtered and the solid washed with tetrahydrofuran. The solid is dried in vacuo (60°C, < 1mm) to afford 1.72 g (79%) of N-phthaloyl- β -alanine amide, which can be alternatively named as 3-phthalimidopropionic acid, as a white powder: mp 252-253°C; 1H NMR (DMSO-d₆) δ 8.00-7.70 (m, 4 H, Ar), 7.45 (br s, 1 H, CONH₂), 6.89 (br s, 1 H, CONH₂), 3.78 (t, 2 H, J = 7 Hz, CH₂CO), 2.43 (t, 2 H, CH₂); 13C NMR (DMSO-d₆) δ 171.5, 167.6, 134.2, 131.6, 122.9, 34.1, 33.5. Anal. Calculated for C₁₁H₁₀N₂O₃. Theoretical: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.49; H, 4.59; N, 12.82.

25

EXAMPLE 18

To a stirred solution of glycaminamide hydrochloride (2.20 g, 20.0 mmol) and sodium carbonate (2.54 g, 24 mmol) in 25 mL of water is added N-carbethoxyphthalimide (4.38 g, 20.0 mmol). The resulting suspension is stirred for 1.5 hour and then filtered to afford 3.22 g (79%) of crude product as a white powder. The crude product is slurried in 200 mL of refluxing ethanol and, after cooling to room temperature, the resulting suspension is filtered and the solid dried in vacuo (60°C, < 1mm) to afford 2.65 g (65%) of N-phthaloylglycaminamide, which

can be alternatively named as phthalimidoacetamide, as a white powder: mp 199-201°C; ¹H NMR (DMSO-d₆) δ 8.00-7.8 (m, 4 H, Ar), 7.70 (br s, 1 H, CONH₂), 7.26 (br s, 1 H, CONH₂), 4.16 (s, 2 H, CH₂); ¹³C NMR (DMSO-d₆) δ 167.8, 167.5, 134.4, 131.7, 123.1, 39.9. Anal. Calculated for C₁₁H₁₀N₂O₃. Theoretical: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.49; H, 4.59; N, 12.82.

5

EXAMPLE 19

By following the procedure of Example 17 but utilizing an equivalent amount of 4-aminobutyric acid, there is obtained a 10 67% yield of 4-phthalimidobutyric acid as a white powder: mp 108-111°C; ¹H NMR (DMSO-d₆) δ 12.10 (s, 1 H), 7.92-7.75 (m, 4 H, Ar), 3.62 (t, J = 6.8 Hz, 2 H), 2.29 (t, J = 7.2 Hz, 2 H), 1.90-1.76 (m, 2 H); ¹³C NMR (DMSO-d₆) δ 173.8, 167.9, 134.2, 131.6, 122.9, 36.8, 30.9, 23.3.

15

EXAMPLE 20

By following the procedure of Example 15 but utilizing an equivalent amount of 4-phthalimidobutyric acid, there is obtained 4-phthalimidobutyramide as a white powder in a 23% 20 yield: mp 159.5-161.5°C; ¹H NMR (DMSO-d₆) δ 8.0-7.7 (m, 4 H, Ar), 3.58 (t, J = 6.9 Hz, 2 H), 2.09 (t, 2 H), 1.92-1.70 (m, 2 H); ¹³C NMR (DMSO-d₆) δ 173.3, 167.9, 134.2, 131.6, 122.9, 37.1, 32.3, 23.9.

EXAMPLE 21

By following the procedure of Example 18 but employing N-carbethoxyphthalimide and (S)-phenylalaninamide hydrochloride, 25 there is obtained (S)-2-phthalimido-3-phenylpropionamide which can be recrystallized from ethanol to afford white crystals: mp 211-215°C; ¹H NMR (DMSO-d₆) δ 7.92 (s, 5 H, Ph), 7.72, 7.33 (2 s, 2 H), 7.2-7.0 (m, 4 H, Ar), 4.92 (dd, 1 H, J = 12, 4.5 Hz), 3.52 (dd, 1 H, J = 4.3, 13.9), 3.35 (dd, 1 H, J = 12, 13.9); ¹³C NMR (DMSO-d₆) δ 169.6, 167.4, 137.7, 134.3, 131.2, 128.5, 128.1, 126.3, 122.9, 54.2, 33.7.

EXAMPLE 22

To a stirred solution of d,l-phenylalanine (4.17 g, 25.0 mmol) and sodium carbonate (2.78 g, 26.25 mmol) in 50 mL of water is added N-carboethoxyphthalimide (5.65 g, 25.0 mmol).
5 The resulting slurry is stirred for 1.5 hour and filtered. The pH of the filtrate is adjusted to 1-2 with 4 N hydrochloric acid with stirring. After 20 minutes, the slurry is refiltered and the solid washed with water. The solid is dried in vacuo (60°C, < 1mm) to afford 5.44 g (74%) of 2-phthalimido-3-phenylpropionic acid as a white powder: mp 165-169°C; 1H NMR (DMSO-d₆, 250 MHz) δ 12.5(br s, 1H), 7.84(s, 4H), 7.23-7.06 (m, 5H), 5.13 (dd, 1H, J = 5.0), 3.26-3.05 (m, 2H); 13C NMR (250 MHz, DMSO-d₆) δ 170.0, 167.0, 137.2, 134.8, 130.6, 128.6, 128.2, 126.5, 123.3, 52.8, 33.8. Anal. Calculated for C₁₇H₁₃NO₄. Theoretical: C, 69.15; H, 4.44; N, 4.74.
10 Found: C, 69.07; H, 4.34; N, 4.78.
15

EXAMPLE 23

To a stirred solution of 2-phthalimido-3-phenylpropionic acid (2.95 g, 10.0 mmol) in tetrahydrofuran (25 mL) are added carbonyldiimidazole (1.62 g, 10.0 mmol) and a few crystals of 4-N,N-dimethylaminopyridine, followed by 15 mL of tetrahydrofuran. The reaction mixture is stirred at room temperature for 45 minutes and 1 mL of concentrated ammonium hydroxide then is added. After 10 minutes, the reaction mixture is diluted with 50 mL water and the resulting slurry is partially concentrated to remove the tetrahydrofuran and filtered. The solid is washed with water and dried in vacuo (60°C, < 1mm) to afford 2.46 g (84%) of 2-phthalimido-3-phenylpropionamide as a white powder: mp 224-226°C; 1H NMR (DMSO-d₆, 250 MHz) δ 7.79 (s, 4 H, Ar), 7.71 (br s, 1 H, CONH₂), 7.32 (br s, 1 H, CONH₂), 7.20-7.02 (m, 5H, Ar), 5.06-4.98 (m, 1H), 3.56-3.25 (m, 2H); 13C NMR (DMSO-d₆, 250 MHz) δ: 169.6, 168.0, 137.1, 134.3, 131.2, 129.5, 128.1, 126.3, 122.9, 54.2, 33.7. Anal. Calculated for C₁₇H₁₄N₂O₃. Theoretical: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.37; H, 4.73; N, 9.43.
20
25
30
35

EXAMPLE 24

To a stirred solution of 4-fluorophenylglycine (3.38 g, 20.0 mmol) and sodium carbonate in 450 mL of 2:1 water:acetonitrile is added N-carbethoxyphthalimide (4.38 g, 20 mmol). After 1 hour, the reaction mixture is partially concentrated to remove the acetonitrile. The resulting slurry is filtered and the pH of the stirred filtrate is adjusted to 1-2 with 4 N hydrochloric acid and then stirred for an additional 30 minutes and filtered. The solid is air-dried and then dried in vacuo (60°C, < 1 mm) to afford 4.55 g (76%) of 2-phthalimido-2-(4-fluorophenyl)acetic acid as a white powder: mp 180-183°C; 1H NMR (DMSO-d₆, 250 MHz) δ 8.10-7.80 (m, 4 H), 7.65-7.45 (m, 4 H), 7.3-7.10 (t, 2 H), 6.10 (s, 1 H); 13C NMR (DMSO-d₆, 250 MHz) δ 168.9, 166.9, 163.6, 159.7, 135.0, 131.4, 131.3 (m), 130.9, 123.5, 115.0, 114.7, 54.4. Anal. Calculated for C₁₆H₁₀NO₄F. Theoretical: C, 64.22; H, 3.37; N, 4.68. Found: C, 64.13; H, 3.33; N, 4.63.

Similarly prepared from 2-fluorophenylglycine is 2-phthalimido-2-(2-fluorophenyl)acetic acid as a white solid: mp 174.5-180.5°C; 1H NMR (DMSO-d₆) δ 13.8 (br s, 1 H), 7.65-7.15 (m, 4H), 6.18 (s, 1 H); 13C NMR (DMSO-d₆) δ 168.1, 166.8, 162.1, 158.2, 135.0, 130.9, 130.8, 130.5, 130.4, 124.1, 123.6, 121.8, 121.6, 115.3, 114.9, 48.9. Anal. Calculated for C₁₆H₁₀NO₄F. Theoretical: C, 64.22; H, 3.37; N, 4.68. Found: C, 63.93; H, 3.27; N, 4.68.

EXAMPLE 25

Similarly prepared according to the procedure of Example 23 from 2-phthalimido-2-(4-fluorophenyl)acetic acid, carbonyldiimidazole, 4-N,N-dimethylaminopyridine and concentrated ammonium hydroxide is 2-phthalimido-2-(4-fluorophenyl)acetamide which can be recrystallized from tetrahydrofuran to afford 0.76 g (51%) of the product as white crystals: mp 180-183°C; 1H NMR (DMSO-d₆) δ 8.00-7.55 (m, 4 H), 7.64 (s, 1 H), 7.60-7.40 (m, 3 H), 7.25-7.05 (m, 2 H), 5.83 (s, 1 H). Anal.

Calculated for $C_{16}H_{11}N_2O_3F$. Theoretical: C, 64.43; H, 3.72; N, 9.39. Found: C, 64.16; H, 3.62; N, 9.18.

Likewise from 2-phthalimido-2-(2-fluorophenyl)acetic acid there is obtained 2-phthalimido-2-(2-fluorophenyl)acetamide as small white crystals: mp 197-201°C; 1H NMR (DMSO-d₆) δ 8.05-7.75 (m, 5 H), 7.65-7.05 (m, 5 H), 6.06 (s, 1 H), ^{13}C NMR (DMSO-d₆) δ 167.4, 166.9, 162.2, 158.3, 134.6, 131.3, 131.2, 131.1, 130.2, 130.0, 123.9, 123.8, 123.2, 122.4, 115.1, 114.8, 49.9.

10

EXAMPLE 26

To a stirred solution of d,l-leucine (3.31 g, 25.0 mmol) and sodium carbonate (2.78 g, 26.25 mmol) in 50 mL of water is added N-carboethoxyphthalimide (5.65 g, 25.0 mmol). After 1 hour at room temperature, the reaction slurry is filtered, the filtrate stirred, and the pH adjusted to 1-2 with 4 N hydrochloric acid. The mixture is stirred overnight, the resulting slurry is filtered, and the solid washed with water and dried in vacuo (60°C, < 1mm) to afford 5.32 g (81%) of the 2-phthalimido-4-methylpentanoic acid as a white powder: mp 134-137°C; 1H NMR (DMSO-d₆, 250 MHz) δ 12.50 (br s, 1H), 8.00-7.80 (m, 4H), 4.79 (dd, 1H, J = 4.3), 2.28-2.10 (m, 1H), 1.94-1.77 (m, 1H), 1.51-1.34 (m, 1H), 0.89 (d, 3H, J = 4.4), 0.86 (d, 3H, J = 4.5); ^{13}C NMR (DMSO-d₆) δ 170.8, 167.4, 134.8, 131.1, 123.3, 50.2, 36.7, 24.6, 23.0, 20.8. Anal. Calculated for $C_{14}H_{15}NO_4$. Theoretical: C, 64.36; H, 5.74; N, 5.36. Found: C, 64.18; H, 5.73; N, 5.98.

EXAMPLE 27

To a stirred solution of 2-phthalimido-4-methylpentanoic acid (1.32 g, 5.0 mmol) in tetrahydrofuran (25 mL) are added carbonyldiimidazole (0.81 g, 5.0 mmol) and a few crystals of 4-N,N-dimethylaminopyridine followed by 15 mL of tetrahydrofuran. The reaction mixture is stirred at room temperature for 1 hour, then 1 mL of concentrated ammonium hydroxide is

added. After 10 minutes, the reaction mixture is diluted with 50 mL water. The resulting slurry is partially concentrated to remove the tetrahydrofuran and filtered. The solid is washed with water and dried in vacuo (60°C, < 1mm) to afford 5 1.16 g (89%) of 2-phthalimido-4-methylpentanamide as a white powder: mp 173-176°C; 1H NMR (DMSO-d₆, 250 MHz) δ 7.95-7.79 (m, 4 H, Ar), 7.61 (br s, 1 H, CONH₂), 7.22 (br s, 1 H, CONH₂), 4.73-4.60 (m, 1 H), 2.30-2.10 (m, 1 H), 1.95-1.80 (m, 1H), 1.45-1.25 (m, 1H); 13C NMR (DMSO-d₆) δ: 170.4, 167.7, 10 134.4, 131.5, 123.1, 51.3, 36.4, 24.7, 23.2, 20.6. Anal. Calculated for C₁₄H₁₆N₂O₃. Theoretical: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.63; H, 6.11; N, 10.70.

EXAMPLE 28

15 To a stirred solution of histidine (3.17 g, 20.0 mmol) and sodium carbonate (2.23 g, 21 mmol) in 50 mL of water is added N-carboethoxyphthalimide (4.52 g, 20.0 mmol). After 1.5 hour, the reaction slurry is filtered. The filtrate is stirred and the pH adjusted to 1-2 with 4 N hydrochloric acid. The resulting slurry is filtered and the solid washed with 20 water and dried in vacuo (60°C, < 1mm) to afford 3.65 g (64%) of 2-phthalimido-3-(imidazol-4-yl)propionic acid as a white powder: mp 280-285°C; 1H NMR (DMSO-d₆, 250 MHz) δ 12.5 (br s, 1H), 7.90-7.60 (m, 6H), 6.80(s, 1H), 4.94 (t, 1H, J = 7.8), 3.36 (d, 2H, J = 7.8); 13C NMR (DMSO-d₆) δ 170.1, 167.1, 25 134.8, 134.6, 133.2, 131.1, 123.2, 116.3, 52.4, 25.8; Anal. Calculated for C₁₄H₁₁N₃O₄. Theoretical: C, 58.95; H, 3.89; N, 14.73. Found: C, 58.80; H, 3.88; N, 14.66.

EXAMPLE 29

30 To a stirred mixture of 3-amino-3-(4-methoxyphenyl)-propionic acid (1.95 g, 10.0 mmol) and sodium carbonate (1.11 g, 10.5 mmol) in 200 mL of acetonitrile-water 1:1 is added N-carboethoxyphthalimide (2.26 g, 10.0 mmol). After 1 hour, the reaction slurry is filtered. The filtrate is concentrated to remove the acetonitrile and the pH adjusted to 1-2 with 4 N

hydrochloric acid and stirred over night. The resulting slurry is filtered and the solid washed with water. The solid is dried in vacuo (60 C, < 1mm) to afford 2.82 g (87%) of the 3-phthalimido-3-(4-methoxyphenyl)propionic acid as a white powder: mp 160-164°C; 1H NMR (DMSO-d₆, 250 MHz) δ 12.5 (br s, 1H), 7.95-7.80 (m, 4 H), 7.36 (d, 2 H, J = 8.7), 6.92 (d, 2 H, J = 8.4 Hz), 5.18-5.10 (m, 1 H), 3.70-3.15 (m, 2 H); 13C NMR (DMSO-d₆) δ 171.7, 167.6, 158.6, 134.6, 131.0, 130.8, 128.3, 123.1, 113.9, 55.0, 49.6, 35.9. Anal. Calculated for C₁₈H₁₅NO₅. Theoretical: C, 66.46; H, 4.63; N, 4.31. Found: C, 66.25; H, 4.65; N, 4.28.

Similarly from 3-amino-3-(3-methoxyphenyl)propionic acid there is obtained 3-phthalimido-3-(3-methoxyphenyl)propionic acid as white crystals: mp 111-115°C; 1H NMR (DMSO-d₆, 250 MHz) δ 12.5 (br s, 1H), 7.94-7.81 (m, 4 H), 7.32-7.23 (m, 1H), 7.02-6.85 (m, 3 H), 5.70-5.60 (m, 1 H), 3.77-3.67 (s, 3H), 3.56-3.15 (m, 2 H); 13C NMR (DMSO-d₆) δ 171.6, 167.6, 159.2, 140.4, 134.7, 131.0, 129.7, 123.2, 119.0, 112.9, 112.7, 54.9, 50.0, 35.8.

Likewise from 3-amino-3-(2-methoxyphenyl)propionic acid there is obtained 3-phthalimido-3-(2-methoxyphenyl)propionic acid as a white powder: mp 163-168°C; 1H NMR (DMSO-d₆, 250 MHz) δ 12.5 (br s, 1H), 7.95-7.80 (m, 4 H), 7.45-6.90 (m, 4H), 6.05-5.92 (m, 1 H), 3.78 (s, 3H) 3.55-3.05 (m, 2 H); 13C NMR (DMSO-d₆) δ 171.7, 167.5, 156.1, 134.5, 131.0, 128.9, 127.3, 126.1, 123.0, 120.1, 111.0, 55.5, 45.3, 35.1.

EXAMPLE 30

By following the procedure of Example 27 utilizing 3-phthalimido-3-(4-methoxyphenyl)propionic acid, there is obtained 3-phthalimido-3-(4-methoxyphenyl)propionamide as a white powder: mp 183-188°C; 1H NMR (DMSO-d₆, 250 MHz) δ 7.90-7.75 (m, 4 H, Ar), 7.58 (br s, 1 H, CONH₂), 7.38 (d, 2H, J = 8.6), 6.91 (d, 3H, J = 8.6), 5.73 (t, 1H, J = 7.8), 3.23(d, 2H, J = 7.9); 13C NMR (DMSO-d₆) δ: 171.2, 167.6, 158.5, 134.5,

131.3, 131.2, 128.4, 123.0, 113.7, 55.0, 49.9, 36.8.. Anal. Calculated for $C_{18}H_{16}N_2O_4$. Theoretical: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.27; H, 5.04; N, 8.40.

EXAMPLE 31

5 To a stirred mixture of 3-amino-3-(4-cyanophenyl)-propionic acid (3.80 g, 20.0 mmol) and sodium carbonate (2.23 g, 21 mmol) in 100 mL of water is added N-carboethoxyphthalimide (4.52 g, 20.0 mmol). After 2 hour, the reaction slurry is filtered and the pH of the stirred filtrate adjusted to 1-2 with 4 N hydrochloric acid. The resulting gel is extracted with ethyl acetate (3x 30 mL). The extract is dried over magnesium sulfate and concentrated in vacuo. The crude product is recrystallized from 10% aqueous acetonitrile and then recrystallized from 20% aqueous methanol. The product is dried in vacuo ($60^{\circ}C$, < 1mm) to afford 1.5 g (23%) of 3-phthalimido-3-(4-cyanophenyl)propionic acid as a white powder: mp 134-137°C; 1H NMR (DMSO- d_6 , 250 MHz) δ 12.5 (br s, 1H), 7.95-7.56 (m, 8 H), 5.76 (t, 1 H, J = 7.7), 3.57-3.15 (m, 2 H); ^{13}C NMR (DMSO- d_6) δ 171.5, 167.6, 144.2, 134.8, 132.6, 131.1, 128.1, 123.3, 118.5, 49.7, 35.5.

10

15

20

Likewise from 3-amino-3-(3-cyanophenyl)propionic acid there is obtained 3-phthalimido-3-(3-cyanophenyl)propionic acid as a white powder: mp 172-175°C; 1H NMR (DMSO- d_6 , 250 MHz) δ 12.5 (br s, 1H), 8.05-7.51 (m, 8 H), 5.82-5.70 (m, 1 H), 3.63-3.20 (m, 2 H); ^{13}C NMR (DMSO- d_6) δ 171.5, 167.6, 140.3, 134.6, 132.0, 131.5, 131.2, 130.7, 129.8, 123.22, 118.5, 111.6, 49.3, 35.6.

25

EXAMPLE 32

30 By following the procedure of Example 27 utilizing 3-phthalimido-3-(4-cyanophenyl)propionic acid, there is obtained 3-phthalimido-3-(4-cyanophenyl)propionamide as a white powder: 1H NMR (DMSO- d_6 , 250 MHz) δ 8.05-7.50 (m, 9 H), 6.97 (s, 1 H), 5.87-5.72 (m, 1 H), 3.44-3.12 (m, 2 H); ^{13}C NMR (DMSO- d_6) δ

170.8, 167.6, 144.6, 134.6, 132.4, 131.1, 127.9, 123.2, 118.5;
110.3, 49.8, 36.4.

Similarly from 3-phthalimido-3-(3-cyanophenyl) propionic acid (1.60 g, 5.0 mmol), there is obtained 3-phthalimido-3-(3-cyanophenyl)propionamide as a white powder: mp 217-220°C; 1H NMR (DMSO-d₆, 250 MHz) δ 8.05-7.40 (m, 9 H), 6.99 (br s, 1 H), 5.90-5.75 (m, 1H), 3.50-3.10 (m, 2H); 13C NMR (DMSO-d₆) δ: 171.0, 167.7, 140.8, 134.6, 132.2, 131.5, 131.4, 130.8, 129.9, 123.2, 118.7, 111.5, 49.7, 36.7.

10

EXAMPLE 33

To a stirred solution of phenyl isocyanate (2.2 mL, 2.4 g, 20 mmol) in acetonitrile (40 mL) is added a solution of L-glutamine (2.92 g, 20.0 mmol) and sodium hydroxide (20 mmol) in water (20 mL). The reaction mixture is stirred for 45 hours, partially concentrated to remove the acetonitrile, and washed with ethyl acetate (2 x 25 mL). The pH of the aqueous layer is adjusted to 1-2 with 4 N hydrochloric acid, the resulting thick slurry filtered, and the solid washed with water and air-dried to afford 4.70 g (89%) yield of 2-(N-phenyluriedo)-4-carbamoylbutyric acid as a white powder.

2-(N-phenyluriedo)-4-carbamoylbutyric acid (2.00 g, 7.54 mmol) and carbonyldiimidazole (1.24 g, 7.95 mmol) in tetrahydrofuran (30 mL) are heated at reflux for 16 hours. The reaction mixture is concentrated and the residue slurried in water (25 mL), the slurry filtered, and the solid washed with water and air-dried to afford 0.63 g of N-phenyl-N'-(1,6-dioxopiperidin-2-yl)urea. After sitting, filtration of the filtrate afforded 0.70 g (38%) of the product as a white flocculent powder: 1H NMR (DMSO-d₆) δ 8.51 (s, 1 H, CONHCO), 7.6-7.2 (m, 6 H, Ar, ArNH), 6.83 (s, 1 H, NHCH), 4.26 (t, 1 H, CHCO), 2.4-1.8 (m, 4 H, CH₂CH₂); 13C NMR (DMSO-d₆) δ 173.2, 155.6, 132.2, 128.7, 127.7, 126.7, 55.7, 29.8, 27.2. Anal. Calculated for C₁₂H₁₃N₃O₃. Theoretical: C, 58.29; H, 5.29; N, 16.99. Found: C, 58.12; H, 5.17; N, 17.02.

EXAMPLE 34

To a stirred solution of 3-amino-3-(4-methoxyphenyl)-propionic acid methyl ester hydrochloride (1.50 g, 6.1 mmol) and sodium carbonate (90.65 g, 6.1 mmol) in 40 mL of water was added N-carboethoxyphthalimide (1.34 g, 6.1 mmol) in 12 mL of acetonitrile. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was partially concentrated and this mixture was stirred for 72 hours. The resulting slurry was filtered and the solid was washed with copious amount of water. The solid was dried in vacuo (30°C, < 1 mm) to afford 1.70 g (50%) of methyl 3-phthalimido-3-(4-methoxyphenyl)propionate as a white powder. mp 65-66°C; ¹H NMR (DMSO-d₆, 250 MHz) δ 7.83-7.91 (m, 4H), 6.88-7.3 (m, 4H), 5-80 (dd, 1H, J = 7.5, 2.5), 3.72 (s, 3H), 3.54 (s, 3H), 3.2-3.6 (m, 2H); ¹³C NMR (DMSO-d₆) δ 170.7, 167.5, 158.7, 134.6, 131.0, 130.5, 128.3, 123.2, 113.9, 55.0, 51.5, 49.4, 35.4. Anal. Calcd for C₁₉H₁₇NO₅: C, 67.25; H, 5.05; N, 4.13; Found: C, 66.96; H, 5.00; N, 4.11.

EXAMPLE 35

To a stirred solution of 3-amino-3-(4-methoxyphenyl)-propionic acid ethyl ester hydrochloride (1.00 g, 3.85 mmol) and sodium carbonate (0.41g, 3.85 mmol) in 40 mL of water was added N-carboethoxyphthalimide (0.84 g, 3.85 mmol) in 10 mL of acetonitrile. The reaction was complete in one hour by TLC. The reaction mixture was partially concentrated to remove the acetonitrile. To the resulting mixture was added 0.5 mL of Et₂O and the mixture was stirred for 1 hour at room temperature. The resulting slurry was filtered and the solid was washed with copious amounts of water. The solid was air-dried overnight to afford 1.02 g (75%) of ethyl 3-phthalimido-3-(4-methoxyphenyl)propionate as a white gum: mp 32°C; ¹H NMR (DMSO-d₆, 250 MHz) δ 7.86 (m, 4H), 6.90-7.37 (M, 4H), 5.66 (dd, 1H J₁ = 7.5, J₂ = 2.5), 4.00 (d, 2H, J = 7.5), 3.3-3.6 (M, 2H), 1.04 (t, 3H, J = 7.5 Hz); ¹³C (DMSO-d₆) δ 170.1, 167.5, 158.7, 134.7, 131.0, 130.5, 128.3, 123.2, 113.88, 60.1.

55.0, 49.5, 35.7, 13.8. Anal. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.90; Found C, 67.78; H, 5.30; N, 3.92.

EXAMPLE 36

To a stirred solution of 3-amino-3-phenylpropionic acid methyl ester hydrochloride (0.50 g, 2.3 mmol) and sodium carbonate (0.25 g, 2.3 mmol) in 10 mL of water was added N-carboethoxyphthalimide (0.51 g, 2.3 mmol) in 7 mL of acetonitrile. The reaction progress was monitored by TLC (ethyl acetate/hexane; 1:2) which showed that the reaction was complete in one hour. The reaction mixture was partially concentrated to remove the acetonitrile. The resulting slurry was filtered and the solid was washed with 20 mL of water. The solid was dried in vacuo ($60^\circ C$, < 1 mm) to afford 280 mg (39.4%) of methyl 3-phthalimido-3-phenylpropionate as a white powder: mp 75-76°C; 1H NMR (DMSO-d₆, 250 MHz) δ 7.26-7.83 (m, 9H), 5.68-5.75 (m, 1H), 3.55 (s, 3H), 3.37-3.66 (m, 2H); ^{13}C NMR (DMSO-d₆) δ 170.7, 167.6, 138.6, 134.7, 131.0, 128.6, 127.8, 126.9, 123.3, 51.6, 49.9, 35.3. Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53; Found: C, 69.69; H, 4.83; N, 4.49.

EXAMPLE 37

To a stirred solution of 3-amino-3-(4'-methoxyphenyl)-propionic acid propyl ester hydrochloride (1.50 g, 5.52 mmol) and sodium carbonate (0.59g, 5.52 mmol) in 50 mL of water was added N-carboethoxy-phthalimide (1.21 g, 5.52 mmol) in 12 mL of acetonitrile. The reaction was complete in one hour. The acetonitrile was removed in vacuo and 5 mL of ether was added to the mixture, which was stirred overnight at room temperature. The resulting slurry was filtered and the solid was washed with 60 mL of water. The solid was dried in vacuo ($24^\circ C$, < 1 mm) to afford 1.69g (83.2%) of propyl 3-phthalimido-3-(4-methoxyphenyl)propionate as a white powder: mp 51.2-52.8°C; 1H NMR (DMSO-d₆ 250 MHz) δ 7.86 (m, 4H), 6.92-7.33 (m, 4H), 5.66 (dd, 1H, $J_1 = 7.5$, 2.5 Hz), 3.90 (t, 2H,

J = 5 Hz), 3.72 (s, 3H), 3.3-3.63 (m, 2H), 1.42 (hex, 2H, J = 7.5 Hz), 0.75 (t, 3H, J = 7.5 Hz); ^{13}C (DMSO-d₆) δ 170.2, 167.5, 158.7, 134.7, 131.0, 130.5, 128.3, 123.2, 113.9, 65.6; 5 55.0, 49.5, 21.3, 9.98. Anal. Calcd for C₁₉H₁₇NO₅: = C, 68.65; H, 5.76; N, 3.81; Found = C, 68.42; H, 5.49; N, 3.76.

EXAMPLE 38

A stirred mixture of phenylglycine (1.51 g, 10.0 mmol) and phthalic dicarboxaldehyde (1.34 g, 10.0 mmol) in 10 mL of acetic acid under nitrogen was heated to reflux for 10 minutes. The resulting mixture was allowed to cool overnight and the resulting slurry filtered to afford 1.56 g of crude product. The crude product was recrystallized from acetic acid to afford after drying in vacuo (< 1 mm, 60 C) 0.95 g (36%) of 2-(1'-Oxo-isoindoline)-2-phenylethanoic acid as a white powder: 10 1H NMR (DMSO-d₆, 250 MHz) 7.85-7.30 (m, 9 H, Ar), 6.01 (s, 1 H, CH), 4.64 (d, J = 17.4 Hz, 1 H), 3.92 (d, J = 17.4 Hz, 1 H); 13C NMR (DMSO-d₆) 171.2, 167.4, 142.0, 134.6, 131.6, 131.3, 128.9, 128.7, 128.4, 127.9, 123.6, 122.9, 57.9, 47.6; Anal. 15 Calcd for C₁₆H₁₃NO₃ 0.13 H₂O. Theory: C, 71.29; H, 4.95; N, 5.20. Found: C, 71.29; H, 4.86; N, 5.26.

EXAMPLE 39

A mixture of 2-(1'-oxo-isoindoline)-2-phenylethanoic acid (0.50 g, 1.87 mmol) and carbonyl diimidazole (CDI, 0.319 g, 1.96 mmol) in 20 mL of tetrahydrofuran under nitrogen was 25 stirred for 2.5 h, then 0.3 mL of 15 N ammonium hydroxide was added. The resulting mixture was stirred for 20 minutes, concentrated to an oil and diluted with 25 mL of water. The mixture was stirred and the resulting slurry filtered to afford after drying 0.38 g (76%) of 2-(1'-Oxo-isoindoline)-2-phenylacetamide as a white powder: 1H NMR (DMSO-d₆, 250 MHz) 8.10-30 7.20 (m, 11 H), 6.03 (s, 1 H), 4.80 (d, J = 17.7 Hz, 1 H), 3.90 (d, J = 17.7 Hz, 1 H); 13C NMR (DMSO-d₆) 167.4, 142.2, 136.0, 131.5, 131.4, 128.7, 128.5, 128.0, 127.7, 123.4, 122.8,

57.5, 48.0; Anal. Calcd for C₁₆H₁₄N₂O₂: Theory C, 72.17; H, 5.30; N, 10.52. Found: C, 72.00; H, 5.27; N, 10.56.

EXAMPLE 40

5 By following the procedure of Example 38 utilizing d,l-phenylalanine to afford without recrystallization 4.46 g (79%) of 3-Phenyl-2-(1'-oxo-isoindoline)propanoic acid as an off-white solid: ¹H NMR (DMSO-d₆, 250 MHz) 13.16 (br s, 1 H, COOH), 7.70-7.05 (m, 9 H, Ar), 5.17 (dd, J = 11, 4.8 Hz, 1 H), 4.45 (s, 2 H, benzylic H), 3.42 (dd, J = 14.6, 4.8 Hz, 1 H), 10 3.22 (dd, J = 14.6, 11 Hz, 1 H); ¹³C NMR (DMSO-d₆) 171.8, 167.7, 141.8, 137.4, 131.5, 131.4, 128.4, 128.3, 127.8, 126.4, 123.4, 122.8, 54.7, 47.2, 34.6; Anal. Calcd for C₁₇H₁₅NO₃: Theory C, 72.58; H, 5.37; N, 4.98. Found: C, 72.60; H, 5.33; N, 4.91.

15

EXAMPLE 41

20 By following the procedure of Example 39 utilizing 3-phenyl-2-(1'-oxo-isoindoline)propanoic acid to afford 1.13 g (81%) of 3-Phenyl-2-(1'-oxo-isoindoline)propionamide as a fine white powder: ¹H NMR (DMSO-d₆, 250 MHz) 7.90-7.05 (m, 11 H, Ar and CONH₂), 5.16 (dd, J = 11, 5 Hz, 1 H), 5.71 (d, J = 18 Hz, 1 H), 5.45 (d, J = 18 Hz, 1 H), 3.33 (dd, J = 15, 5 Hz, 1 H), 3.11 (dd, J = 11, 15 Hz, 1 H); ¹³C NMR (DMSO-d₆) 172.0, 167.6, 142.0, 137.6, 131.7, 131.3, 128.4, 128.2, 127.6, 126.3, 123.3, 122.7, 54.6, 47.2, 35.3; Anal. Calcd for C₁₇H₁₆N₂O₂: Theory C, 72.84; H, 5.75; N, 9.99. Found: C, 72.72; H, 5.76; N, 9.86.

25

EXAMPLE 42

30 By following the procedure of Example 38 utilizing 3-amino-3-phenylpropanoic acid to afford 0.8 g of crude product. The filtrate was then concentrated and the residue slurried in ethyl acetate to afford an additional 1.39 g of crude product. The combined crude products were recrystallized from ethyl acetate to afford 1.52 (58%) of 3-Phenyl-3-(1'-oxo-isoindo-

line)propanoic acid as fine white crystals: ^1H NMR (DMSO-d₆, 250 MHz) 12.44 (br s, 1 H, CO₂H), 7.80-7.15 (m, 9 H, Ar), 5.79 (overlapping dd, 1 H), 4.54 (d, J = 17.6 Hz, 1 H), 4.15 (d, J = 17.6 Hz, 1 H), 3.35-3.0 (m, 2 H); ^{13}C NMR (DMSO-d₆) 171.8, 166.9, 141.6, 139.3, 132.0, 131.4, 128.6, 127.9, 127.6, 127.0, 123.4, 122.8, 51.3, 46.3, 36.6; Anal. Calcd for C₁₇H₁₅NO₃: Theory C, 72.58; H, 5.37; N, 4.90. Found: C, 72.23; H, 5.29; N, 4.90.

EXAMPLE 43

To a stirred solution of 3-phenyl-3-(1'-oxo-isoindoline)-propanoic acid (0.703 g, 2.50 mmol) in 15 mL of tetrahydrofuran under nitrogen was added carbonyldiimidazole (0.438 g, 2.70 mmol), and a few crystals of 4-N,N-dimethylaminopyridine [DMAP]. The reaction mixture was stirred for 1.5 hours and then 0.25 mL of 15 N ammonium hydroxide was added. After 20 minutes, the reaction mixture was concentrated in vacuo and the residue slurried in water. The resulting solid was isolated by filtration and dried in vacuo to afford 0.58 g (80%) of crude product as an off-white powder. The crude product was recrystallized from Ethanol to afford 0.403 g (57%) of 3-Phenyl-3-(1'-oxo-isoindoline)propanamide as white prisms: ^1H NMR (DMSO-d₆, 250 MHz) 7.8-7.2 (m, 10 H), 6.92 (br s, 1 H), 5.81 (overlapping dd, 1 H) 4.59 (d, J = 17.5 Hz, 1 H), 4.16 (d, J = 17.5 Hz, 1 H), 3.1-2.8 (m, 2 H); ^{13}C NMR (DMSO-d₆) 171.3, 167.0, 140.7, 132.2, 131.4, 128.6, 127.9, 127.5, 126.9, 123.5, 122.8, 51.5, 46.3, 37.9; Anal. Calcd for C₁₇H₁₆N₂O₂: Theory C, 72.84; H, 5.75; N, 9.99. Found: C, 72.46; H, 5.68; N, 9.91.

EXAMPLE 44

By following the procedure of Example 38 utilizing 3-amino-3-(4'-methoxyphenyl)propanoic acid to afford 1.52 g of crude product as an off white solid from the reaction mixture. The filtrate was concentrated and the residue slurried in 25 mL of ethyl acetate to afford after filtration an additional

1.27 g. (41%) of crude product as a pale green powder. The combined crude products were recrystallized from 280 mL of ethyl acetate to afford after drying 1.69 g (55%) of 3-(4'-Methoxyphenyl)-3-(1'-oxo-isoindoline)propanoic acid as an off-white solid: 1H NMR (DMSO-d₆, 250 MHz); 13C NMR (DMSO-d₆); Anal. Calcd for C₁₈H₁₇NO₄: Theory C, 69.44; H, 5.50; N, 4.50. Found: C, 69.33; H, 5.45; N, 4.49.

EXAMPLE 45

By following the procedure of Example 43 utilizing 3-(4'-methoxyphenyl)-3-(1'-oxo-isoindoline)propanoic acid to afford 0.49 g (82%) of crude product. The crude product was recrystallized from ethyl acetate (40 mL) to afford 0.27 g (45%) of 3-(4'-Methoxyphenyl)-3-(1'-oxo-isoindoline)propionamide as white needles: 1H NMR (DMSO-d₆, 250 MHz) 7.8-7.4 (m, 5 H), 7.29 (d, 2 H, J = 9 Hz), 6.91 (d, 2 H, J = 9 Hz), 5.78 (t, 1 H, J = 8 Hz), 4.55 (d, 1 H, J = 17.5 Hz), 4.11 (d, J = 17.5 Hz, 1 H), 3.72 (s, 3 H), 3.05-2.75 (m, 2 H); 13C NMR (DMSO-d₆) 171.2, 166.8, 158.4, 141.6, 132.2, 131.8, 131.2, 128.1, 127.8, 123.3, 122.7, 113.8, 55.0, 51.0, 46.1; Anal. Calcd for C₁₈H₁₈N₂O₃-0.38 H₂O: Theory C, 68.58; H, 5.99; N, 8.80. Found: C, 68.58; H, 5.86; N, 8.80.

EXAMPLE 46

By following the procedure of Example 38 utilizing 3-amino-3-(3',4'-dimethoxyphenyl)propanoic acid with the following exceptions. The reaction mixture (solution) was concentrated to a thick oil which was diluted with 10 mL of ethyl acetate. The resulting slurry was filtered, the solid washed with ethyl acetate and then dried in vacuo (> 1 mm, 60 C) to afford 2.77 g (81%) of 3-(3',4'-Dimethoxyphenyl)-3-(1'-oxo-isoindoline)propanoic acid as a white powder: mp 146.5-148.5 C; 1H NMR (DMSO-d₆, 250 MHz) 12.34 (br s, 1 H, CO₂H), 7.8-7.4 (m, 4 H), 7.1-6.8 (m, 3 H), 5.85-5.65 (m, 1 H), 4.51 (d, 1 H, J = 18 Hz), 4.13 (d, 1 H, J = 18 Hz), 3.75 (s, 3 H), 3.73 (s, 3 H), 3.3-3.0 (m, 2 H); 13C NMR (DMSO-d₆) 171.8, 166.7, 148.7,

148.3, 141.6, 132.1, 131.6, 131.3, 127.8, 123.4, 122.7, 119.2, 111.7, 111.2, 55.5, 55.4, 46.3, 36.8; Anal. Calcd for C₁₉H₁₉NO₅: Theory C, 66.85; H, 5.61; N, 4.10. Found: C, 67.19; H, 5.57; N, 3.73.

5

EXAMPLE 47

By following the procedure of Example 43 utilizing 3-(3',4'-dimethoxyphenyl)-3-(1'-oxo-isoindoline)propanoic acid with the following changes. The crude product did not precipitate from water immediately. The product crystallized from aqueous solution upon sitting for several days after an ether wash to afford 0.26 g (22%) of 3-(3',4'-Dimethoxyphenyl)-3-(1'-oxo-isoindoline)propionamide as white needles: ¹H NMR (DMSO-d₆, 250 MHz) 7.8-7.4 (m, 5H), 7.1-6.85 (m, 4 H), 5.76 (m, 1 H), 4.57 (d, 17.6 Hz, 1 H), 4.15 (d, J = 17.6 Hz, 1 H), 3.74 (s, 3 H), 3.72 (s, 3 H), 3.1-2.8 (m, 2 H); ¹³C NMR (DMSO-d₆) 171.2, 166.8, 148.6, 148.1, 141.6, 132.2, 132.2, 131.2, 127.8, 123.4, 122.7, 119.0, 111.6, 111.0, 55.4, 51.4, 46.2, 37.9; Anal. Calcd for C₁₉H₂₀ON₂O₄: Theory C, 67.05; H, 5.92; N, 8.23. Found: C, 66.74; H, 5.88; N, 8.02.

10

15

20

EXAMPLE 48

25

30

To a stirred solution of 3-amino-3-(3',4'-diethoxyphenyl)propionic acid (1.03 g, 4.07 mmol) and sodium carbonate (0.453 g, 4.27 mmol) in a 1/1 mixture of 150 mL of acetonitrile/water (heated to 45 C to dissolve) was added N-carbethoxyphthalimide (0.89 g, 4.07 mmol). The reaction mixture was stirred 1h, then partially concentrated in vacuo to remove the acetonitrile to afford a pale yellow solution. The stirred solution was acidified to pH 0-1 with 4 N hydrochloric acid to form a gum. The mixture was stirred overnight. The gum had not solidified, 1 mL of ether was added to mixture. The gum solidified on stirring, the slurry was filtered and the solid dried to afford 1.94 g (94%) of 3-(3',4'-Diethoxyphenyl)-3-(phthalimido)propionic acid as a yellow solid: ¹H NMR (DMSO-d₆, 250 MHz) 12.41 (br s, 1 H, COOH), 8.10-7.75 (m,

4 H, Ar), 7.15-6.85 (m, 3 H, Ar), 5.62 (overlapping dd, 1 H), 4.20-3.90 (m, 4 H, 2 OCH₂), 3.51 (dd, 1 H, J = 16.5, 9 Hz), 3.25 (dd, 1 H, J = 16.5, 7 Hz), 1.5-0.9 (m, 6 H, 2 CH₃) ¹³C NMR (DMSO-d₆) 1717, 167.6, 147.9, 147.8, 134.6, 131.3, 131.0, 123.1, 119.4, 113.2, 112.7, 63.8, 63.7, 50.0, 36.0, 14.6, 14.6; Anal. Calcd for C₂₁H₂₁N₀₆: Theory C, 65.79; H, 5.52; N, 3.65. Found: C, 65.54; H, 5.55; N, 3.62.

5

EXAMPLE 49

10 The procedure of Example 48 was followed with the following changes. The reaction mixture concentrated in vacuo and to an oil which was diluted with water (20 mL) and ether (1 mL) and the mixture stirred overnight. The resulting slurry was filtered and the solid dried in vacuo to afford 0.41 g (41%) of crude product. The crude product was recrystallized from ethyl acetate to afford 0.265 g (27%) of 3-(3',4'-Diethoxyphenyl)-3-phthalimidopropionamide as white 15 crystals: ¹H NMR (DMSO-d₆, 250 MHz) 8.00-7.60 (m, 4 H, Ar), 7.55 (br s, 1 H, NH), 7.03 (br s, 1 H, NH), 6.89 (br s, 3 H, Ar), 5.66 (t, 1 H, J = 8 Hz), 4.15-3.85 (m, 4 H), 3.3-3.05 (m, 20 2 H), 1.5-1.15 (m, 6 H); ¹³C NMR (DMSO-d₆) 171.2, 167.6, 147.8, 147.6, 134.5, 131.6, 131.2, 123.0, 119.5, 113.0, 112.7, 63.7, 63.6, 50.2, 36.9, 14.6, 14.6; Anal. Calcd for C₂₁H₂₂N₂O₅: Theory C, 65.96 H, 5.80; N, 7.33. Found: C, 65.45; H, 5.55; N, 7.20.

25

EXAMPLE 50

30 To a stirred solution of sodium carbonate (1.45 g, 13.7 mmol) in 500 mL of water-acetonitrile (1:1, v/v) was added 3-amino-3'-(4-propoxyphenyl)propionic acid (3.05 g, 13.7 mmol) as a solid. The mixture was warmed to 30-40°C to dissolve the solids. The reaction mixture was allowed to cool to room temperature and N-carboethoxyphthalimide (3.00 g, 13.7 mmol) was added and the reaction mixture was stirred for one hour at room temperature. The reaction mixture was then partially concentrated to remove the acetonitrile and the pH of the

resulting solution was adjusted to approximately 3 with 4N hydrochloric acid. The resulting slurry was stirred overnight and then filtered and the solid was washed with copious amounts of water. The solid was dried in vacuo (60°C, <1mm) to afford 3.64 g (75%) of 3-Phthalimido-3-(4'-propoxyphenyl)-propionic acid as a white powder: mp 142.5-143.6°C, 1H NMR(DMSO-d₆, 250 MHz) δ 12.43 (br s, 1 H), 7.80-7.95 (m, 4 H), 7.34 (d, 2 H, J = 9 Hz), 6.89 (d, 2 H, J = 9 Hz), 5.63 (overlapping dd, 1 H), 3.88 (t, 2 H, J = 7 Hz), 3.45 (dd, 1 H, J₁ = 9 Hz, J₂ = 16.5 Hz), 3.30 (dd, 1 H, J₁ = 7 Hz, J₂ = 16.5 Hz), 1.60-1.85 (m, 2 H), 0.95 (t, 3 H, J = 7 Hz); 13C (DMSO-d₆) δ 171.8, 167.6, 158.6, 134.7, 131.1, 130.8, 128.3, 123.2, 114.4, 68.9, 49.7, 36.0, 22.0, 10.3; Anal. Calcd. for C₂₀H₁₉NO₅. Theoretical: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.90; H, 5.40; N, 4.00.

EXAMPLE 51

To a stirred solution of 3-phthalimido-3'(4-propoxyphenyl)propionic acid (1.41 g, 4.0 mmol) in 25 mL of under nitrogen was added carbonyldiimidazole (0.68 g, 4.2 mmol) followed by a catalytic amount of dimethylaminopyridine. The mixture was stirred for 45 minutes at room temperature. To the reaction mixture was then added concentrated ammonium hydroxide (0.29 mL, 4.4 mmol) and the reaction mixture was stirred for 30 minutes at room temperature. The mixture was then diluted with 10 mL of water and the tetrahydrofuran was removed in vacuo. The resulting slurry was filtered and the solid was washed with copious amounts of water. The solid was dried in vacuo (60°C, < 1mm) to afford 1.2 g of crude product. The crude product was purified by dissolving in 200 mL of ethyl acetate, stirring for 3h and then concentrating to an 80 mL volume. The resulting slurry was filtered and the solid was washed with ethyl acetate (2x20 mL). The solid was air-dried to afford 0.513 g (36%) of 3-Phthalimido-3-(4'-propoxyphenyl)propionamide as a white powder: mp 109.5-110.4°C; 1H NMR (DMSO-d₆, 250 MHz) δ 7.85 (br s, 4 H), 7.55 (br s, 1 H), 7.33 (d, 2 H, J = 8 Hz), 6.75-7.00 (m, 3 H), 5.69

(t, 1 H, J = 8 Hz), 3.88 (t, 2 H, J = 6 Hz), 3.10-3.30 (m, 2 H), 1.60-1.80 (m, 2 H), 0.95 (t, 3 H, J = 7 Hz); ^{13}C NMR (DMSO-d₆) δ 171.2, 167.7, 158.0, 134.5, 131.23, 131.19, 128.4, 123.1, 114.3, 68.9, 49.9, 36.9, 22.0, 20.4, 10.4; Anal. Calcd. for C₂₀N₂O₄ @0.37 H₂O. Theoretical: C, 66.90; H, 5.61; N, 7.80. Found: C, 66.90; H, 5.52; N, 7.75.

EXAMPLE 52

To 40 mL of stirred ethanol at 0°C under nitrogen was slowly added thionyl chloride (3.3 mL, 45 mmol) followed by addition of 3-amino-3-(3'-pyridyl)propionic acid (2.65 g, 15 mmol). The reaction mixture was allowed to slowly warm to room temperature and then refluxed for 3 hours. After 2 hours at reflux all of the solid had dissolved. The reaction mixture was allowed to cool to room temperature and stirred overnight. The slurry was filtered and the solid was washed with copious amounts of Ethanol. The solid was dried in vacuo (60°C, <1mm) to afford 3.17 g (79%) of Ethyl 3-amino-3-(3'-pyridyl)-propionate hydrochloride as a white powder: ^1H NMR (DMSO-d₆, 250 MHz) δ 9.32 (br s, 3 H), 9.21 (br s, 1 H), 8.87-8.95 (m, 2 H), 8.09-8.14 (m, 1 H), 4.93 (br s, 1 H), 3.90-4.15 (m, 2 H), 3.20-3.38 (m, 2 H), 1.11 (t, 3 H, J = 7 Hz); ^{13}C NMR (DMSO-d₆) δ 168.8, 144.5, 142.8, 142.6, 136.2, 126.7, 60.7, 47.9, 37.2, 13.9.

EXAMPLE 53

By following the procedure of Example XX utilizing Prepared as described earlier for ethyl 3-phthalimido-3-(4'-methoxyphenyl)propionate from ethyl 3-amino-3-(3'-pyridyl)-propionate hydrochloride. Ethyl 3-phthalimido-3-(3'-pyridyl)-propionate was isolated as a white powder (0.43 g, 71%): mp 72.3-72.8°C; ^1H NMR (DMSO-d₆, 250 MHz) δ 8.45-8.70 (m, 2 H), 7.80-8.00 (m, 5 H), 7.35-7.45 (m, 1 H), 5.78 (dd, 1 H, J₁= 6.5 Hz, J₂ = 9.5 Hz), 4.01 (q, 2 H, J = 7 Hz), 3.62 (dd, 1 H, J₁= 6.5 Hz, J₂ = 16.4 Hz), 3.41 (dd, 1 H, J₁= 9.5 Hz, J₂ = 16.4 Hz), 1.05 (t, 3 H, J = 7 Hz); ^{13}C NMR (DMSO-d₆) δ 169.9,

167.5, 148.96, 148.4, 134.9, 134.7, 134.0, 131.0, 123.6,
123.3, 60.3, 47.9, 35.2, 13.8; Anal. Calcd. for C₁₈H₁₆N₂O₄.
Theoretical: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.51; H,
4.94; N, 8.56.

5

EXAMPLE 54

By following the procedure of Example 50 utilizing 3-amino-3-(3',4'-dimethoxyphenyl)propionic acid. 3-Phthalimido-3-(3',4'-dimethoxyphenyl)propionic acid was isolated as a white powder (5.30 g, 75%): 1H NMR (DMSO-d₆, 250 MHz) δ 12.44 (br s, 1 H), 7.70-8.00 (m, 4 H), 6.85-7.10 (m, 3 H), 5.63 (dd, 1 H, J₁ = 7 Hz, J₂ = 9 Hz), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.53 (dd, 1 H, J₁ = 9 Hz, J₂ = 16.5 Hz), 3.26 (dd, 1 H, J₁ = 7 Hz, J₂ = 16.5 Hz), 13C NMR (DMSO-d₆) δ 171.8, 167.7, 148.6, 148.4, 134.7, 131.3, 131.1, 123.2, 119.3, 111.7, 111.0, 55.48, 55.46, 50.1, 36.1.

EXAMPLE 55

By following the procedure of Example 51 utilizing 3-phthalimido-3-(3,4'-dimethoxyphenyl)propionic acid. 3-Phthalimido-3-(3',4'-dimethoxyphenyl)propionamide was isolated as a white powder (0.314 g, 52%): mp 188.8-190.0°C; 1H NMR (DMSO-d₆, 250 MHz) δ 7.7-8.0 (m, 4 H), 7.54 (br s, 1 H), 6.7-7.1 (m, 4 H), 5.67 (t, 1 H, J = 8 Hz), 3.73 (s, 3 H), 3.72 (s, 3 H), 3.20 (d, 2 H, J = 8 Hz); 13C NMR (DMSO-d₆) δ 171.2, 167.7, 148.5, 134.7, 134.5, 131.7, 131.2, 123.1, 119.4, 111.6, 111.2, 55.5, 50.3, 37.0; Anal. Calcd. for C₁₉H₁₈N₂O₅. Theoretical: C, 64.40; H, 5.12; N, 7.91. Found: C, 64.01; H, 5.14; N, 7.64.

EXAMPLE 56

The procedure of Example 52 was followed except the reaction was run at room temperature. Ethyl 3-Amino-3-(3',4'-dimethoxyphenyl)propionate was isolated as a white powder (2.04 g, 88%): 1H NMR (DMSO-d₆, 250 MHz) δ 8.75 (br s, 3 H),

7.30-7.35 (m, 1 H), 6.90-7.05 (m, 2 H), 4.50 (dd, 1 H, J₁ = 6 Hz, J₂ = 9 Hz), 3.90-4.10 (m, 2 H), 3.77 (s, 3 H), 3.75 (s, 3 H), 3.19 (dd, 1 H, J₁ = 6 Hz, J₂ = 16 Hz), 2.98 (dd, 1 H, J₁ = 9 Hz, J₂ = 16 Hz), 1.10 (t, 3 H, J = 7 Hz); ¹³C NMR (DMSO-d₆) δ 169.1, 149.0, 148.6, 128.9, 120.1, 111.4, 60.4, 55.6, 55.5, 50.9, 38.7, 13.9.

EXAMPLE 57

By following the procedure of Example 35 utilizing ethyl 3-amino-3-(3'-pyridyl)propionate. The reaction mixture was concentrated and the residue was dissolved in 20 mL of ethyl acetate and washed with water (3 x 20 mL). The organic phase was dried over sodium sulfate and then concentrated to afford 0.31 g (40%) of ethyl 3-phthalimido-3-(3',4'-dimethoxyphenyl)-propionate as a yellow oil: ¹H NMR (DMSO-d₆, 250 MHz) δ 7.80-7.95 (m, 4 H), 7.04 (s, 1 H), 6.85-6.98 (m, 2 H), 5.65 (dd, 1 H, J₁ = 6 Hz, J₂ = 10 Hz), 4.00 (q, 2 H, J = 7 Hz), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.60 (dd, 1 H, J₁ = 10 Hz, J₂ = 16 Hz), 3.32 (dd, 1 H, J₁ = 6 Hz, J₂ = 16 Hz), 1.05 (t, 3 H, J = 7 Hz); ¹³C NMR (DMSO-d₆) δ 170.2, 167.5, 148.58, 148.54, 134.7, 131.1, 130.9, 123.2, 119.2, 111.6, 111.0, 60.1, 55.5, 50.0, 35.9, 13.9; Anal. Calcd. for C₂₁H₂₁NO₆. Theoretical: C, 65.79; H, 5.52; N, 3.65. Found: C, 65.13; H, 5.73; N, 3.61.

EXAMPLE 58

By following the procedure of Example 51 utilizing 3-phthalimido-3-(3,4'-dimethoxyphenyl)propionic acid and amyl-amine (1.0 equiv) to afford 2.15 g (84%) of crude product. The crude product was dissolved in 150 mL of ethyl acetate and then 50 mL of ether was added and the mixture stirred for 1 hour. The resulting slurry was filtered and the solid dried in vacuo to afford 1.28 g (50%) yield of 3-Phthalimido-3-(3',4'-dimethoxyphenyl)propionic amylamide as a white powder: mp 140.5-142.1°C; ¹H NMR (DMSO-d₆, 250 MHz), δ 8.05 (t, 1 H, J = 5 Hz), 7.85 (m, 4 H), 7.03 (br s, 1 H), 6.90 (m, 3 H), 5.68 (t, 1 H, J = 8 Hz), 3.73 (s, 3 H), 3.71 (s, 3 H), 3.19

(d, 2 H, $J = 8$ Hz), 2.8-3.1 (m, 2 H), 0.9-1.3 (m, 6 H), 0.74 (m, 3 H); ^{13}C NMR (DMSO-d₆) δ 168.8, 167.7, 148.5, 148.3, 134.5, 131.5, 131.2, 123.1, 119.5, 111.6, 111.1, 55.4, 50.6, 38.2, 37.4, 28.7, 28.3, 21.7, 13.7; Anal. Calcd. for C₂₄H₂₈N₂O₅. Theoretical: C, 67.9; H, 6.65; N, 6.60. Found: C, 67.84; H, 6.70; N, 6.57.

EXAMPLE 59

By following the procedure of Example 51 utilizing 3-phthalimido-3-(3,4'-dimethoxyphenyl)propionic acid and benzylamine (1.0 equiv) to afford 2.45 g (92%) of 3-Phthalimido-3-(3',4'-dimethoxyphenyl)propionic benzylamide as white powder: mp. 208.4-209.8°C; ^1H NMR (DMSO-d₆, 250 MHz) δ 8.60 (t, 1 H, $J = 6$ Hz), 7.78-7.92 (m, 4 H), 6.85-7.20 (m, 8 H), 5.73 (t, 1 H, $J = 8$ Hz), 4.10-4.30 (m, 2 H), 3.73 (s, 3 H), 3.72 (s, 3 H), 3.20-3.45 (m, 2 H); ^{13}C NMR (DMSO-d₆) δ 169.1, 167.7, 148.5, 148.3, 139.2, 134.5, 131.4, 131.2, 127.9, 126.7, 123.1, 119.5, 111.5, 111.2, 101.9, 55.4, 55.37, 50.6, 41.7, 37.4; Anal. Calcd. for C₂₆H₂₄N₂O₅. Theoretical: C, 70.26; H, 5.44; N, 6.30. Found: C, 70.12; H, 5.53; N, 6.25.

20

EXAMPLE 60

By following the procedure of Example 51 utilizing 3-phthalimido-3-(3,4'-dimethoxyphenyl)propionic acid and ethylamine (1.0 equiv). After the reaction mixture was concentrated, the residue was diluted with 20 mL of water and 1 mL of ether. The mixture was stirred for 1 hour to afford a slurry. The slurry was filtered and the solid dried in vacuo to afford 0.66 g (77%) of 3-Phthalimido-3-(3',4'-dimethoxyphenyl)propionic ethylamide compound as a white powder: mp 131.0-132.5°C; ^1H NMR (DMSO-d₆, 250 MHz) δ 8.08 (t, 1 H, $J = 5$ Hz), 7.78-7.95 (m, 4 H), 7.03 (s, 1 H), 6.85-7.00 (m, 2 H), 5.69 (t, 1 H, $J = 8$ Hz), 3.74 (s, 3 H), 3.72 (s, 3 H), 3.18 (d, 2 H, $J = 8$ Hz), 2.98 (m, 2 H), 0.88 (t, 3 H, $J = 7$ Hz); ^{13}C NMR (DMSO-d₆) δ 168.8, 167.7, 148.5, 148.2, 134.5, 131.6, 131.2, 123.1, 119.4, 111.6, 111.1, 55.5, 50.5, 37.3,

33.2, 14.5; Anal. Calcd. for $C_{21}H_{22}N_2O_5$. Theoretical: C, 65.96; H, 5.80; N, 7.33. Found: C, 65.85; H, 5.84; N, 7.24.

EXAMPLE 61

By following the procedure of Example 50 utilizing 3-amino-3-(4'-propoxyphenyl)propanoic acid. 3-Phthalimido-3-(4'-ethoxyphenyl)propionic acid was isolated as a white powder (2.52 g, 74%): mp 169.2-171.1°C; 1H NMR (DMSO-d₆, 250 MHz) δ 7.75-8.00 (m, 4 H), 7.34 (d, 2 H, J = 8.7 Hz), 6.89 (d, 2 H, J = 8.7 Hz), 5.64 (overlapping dd, 1 H), 3.98 (q, 2 H, J = 7 Hz), 3.48 (dd, 1 H, J_1 = 9 Hz, J_2 = 16.5 Hz), 3.26 (dd, 1 H, J_1 = 7 Hz, J_2 = 16.5 Hz), 1.30 (t, 3 H, J = 7 Hz); ^{13}C NMR (DMSO-d₆) δ 171.8, 167.7, 158.0, 134.7, 131.1, 130.8, 128.4, 123.2, 114.4, 63.0, 49.7, 36.1, 14.6; Anal. Calcd. for $C_{19}H_{17}NO_5$. Theoretical: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.05, H, 4.93; N, 4.17.

EXAMPLE 62

By following the procedure of Example 51 utilizing 3-phthalimido-3'(4-ethoxyphenyl)propionic acid to afford 1.3 g (88%) of crude product. Recrystallization of the crude material from ethyl acetate afforded 0.28 g (20%) of 3-phthalimido-3-(4'-ethoxyphenyl)propionamide as a white powder: mp 190.6-191.2°C; 1H NMR (DMSO-d₆, 250 MHz) δ 7.75-7.95 (m, 4 H), 7.54 (br s, 1 H), 7.33 (d, 2 H, J = 8.6 Hz), 6.75-6.98 (m, 3 H), 5.69 (t, 1 H, J = 8 Hz), 3.98 (q, 2 H, J = 7 Hz), 3.19 (d, 2 H, J = 8 Hz), 1.30 (t, 3 H, J = 7 Hz); ^{13}C NMR (DMSO-d₆, 250 MHz) δ 167.6, 154.1, 154.2, 130.9, 127.6, 124.7, 119.5, 110.6, 59.4, 46.3, 33.3, 11.0; Anal. Calcd. for $C_{19}H_{18}N_2O_4$ @0.37 H₂O. Theoretical: C, 66.14; H, 5.26; N, 8.12. Found: C, 66.14; H, 5.26; N, 7.81.

EXAMPLE 63

A stirred mixture 3-amino-3-phenylpropionic acid and *cis*-1,2-cyclohexanedicarboxylic anhydride in 10 mL of acetic acid under nitrogen was heated to reflux for 4 h and then allowed to cool to room temperature. The resulting mixture was concentrated to an orange yellow oil. This oil was crystallized from a 1/1 mixture of ethyl acetate/hexane to afford 1.77 g (58%) of 3-(*cis*-hexahydrophthalimido)-3-phenylpropionic acid as white crystals: ^1H NMR (DMSO-d₆) δ 12.45 (br s, 1 H, COOH), 7.33 (m, 5 H, Ph), 5.48 (dd, 1 H, J = 6.3, 9.6, CH), 3.41 (dd, 1 H, J = 16.5, 9.6 Hz), 3.14 (dd, 1H, J = 16.5, 6.3 Hz), 2.50 (m, 2 H), 1.8-1.1 (m, 8 H); ^{13}C NMR (DMSO-d₆) δ 179.3, 179.2, 171.7, 138.7, 128.4, 127.5, 126.8, 50.1, 38.7, 38.6, 35.2, 23.0, 22.9, 21.1. Anal. Calcd for C₁₇H₁₉NO₄. Theory: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.52; H, 6.20; N, 4.60.

EXAMPLE 64

A mixture of 3-(*cis*-hexahydrophthalimido)-3-phenylpropionic acid (0.903 g, 3.00 mmol) and carbonyldiimidazole (0.525 g, 3.75 mmol) in 13 mL of anhydrous tetrahydrofuran under nitrogen was stirred for 1 hour, then 0.25 mL of concentrated ammonium hydroxide was added to the reaction solution. After 20 minutes, the reaction mixture was concentrated in vacuo to an oil. The oil was diluted with 20 mL of water and the mixture extracted with ethyl acetate (20 mL). The organic layer was dried (sodium sulfate) and concentrated to afford an oil. The oil was then purified by flash chromatography (silica gel, 5/95 methanol/methylene chloride, R_f = 0.3) to afford 210 mg of 3-(*cis*-hexahydrophthalimido)-3-phenylpropionamide as an oil which slowly crystallized to an ivory solid: ^1H NMR (DMSO-d₆) 67.49 (s, 1 H, NH), 7.4-7.2 (m, 5 H, Ar), 6.90 (s, 1 H, NH), 5.54 (t, 1 H, J = 7.8 Hz, CH), 3.09 (d, 2 H, J = 7.8 Hz, CH₂), 2.95-2.80 (m, 2 H, CH₂), 1.8-1.1 (m, 8 H); ^{13}C NMR (DMSO-d₆) δ 179.6, 179.5, 171.5, 139.5, 128.6, 127.7, 127.2, 55.2, 50.6, 38.8, 36.5, 23.4, 23.3, 21.5.

EXAMPLE 65

A stirred mixture of 4-methylphthalic acid anhydride (1.62 g, 10.0 mmol) and 3-amino-3-phenylpropionic acid (1.65 g, 10.0 mmol) in 15 mL of acetic acid under nitrogen was heated to reflux for 6 hours. The resulting reaction solution was concentrated in vacuo to an oil which was crystallized from 20 mL of a 1/1 mixture of ethyl acetate/hexane to afford 1.69 g (55%) of 3-(4-methylphthalimido)-3-phenylpropionic acid as an off-white powder: ^1H NMR (DMSO-d₆) δ 12.5 (br s, 1 H, COOH), 7.85-7.55 (m, 3 H, Ar), 7.55-7.2 (m, 5 H, Ar), 5.68 (dd, 1 H, J = 9, 7 Hz, CH), 3.51 (dd, 1 H, J = 9, 16.5 Hz), 3.29 (dd, 1 H, J = 9, 16.5 Hz), 2.47 (s, 3 H, CH₃). Anal. Calcd for C₁₈H₁₅N₁O₄. Theory: C, 69.89, H, 4.89, N, 4.53. Found: C, 69.45, H, 4.93, N, 4.55. HPLC: 95%.

15

EXAMPLE 66

A stirred mixture of cis-5-norbonene-endo-2,3-dicarboxylic anhydride (1.64 g, 10.0 mmol) and 3-amino-3-phenylpropionic acid (1.65 g, 10.0 mmol) in 15 mL of acetic acid under nitrogen was heated to reflux for 6 hours. The resulting reaction solution was concentrated in vacuo to an oil which was crystallized from a 1/1 mixture of ethyl acetate/hexane to afford 2.03 g (65%) of 3-(cis-5-norbonene-endo-2,3-dicarboxylic imide)-3-phenylpropionic acid as a white powder: ^1H NMR (DMSO-d₆) δ 12.41 (br s, 1 H, COOH), 7.29 (m, 5 H, Ph), 6.0-5.7 (m, 2 H), 5.37 (t, 1 H, J = 7.7 Hz), 3.5-3.1 (m, 6 H), 1.49 (m, 2 H); ^{13}C NMR (DMSO-d₆) δ 177.2, 177.1, 171.4, 138.3, 134.3, 134.0, 128.1, 127.5, 127.1, 51.4, 50.1, 44.8, 44.5, 44.4, 35.1. Anal. Calcd for C₈H₁₇NO₄. Theory: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.10; H, 5.33; N, 4.43.

EXAMPLE 67

A stirred mixture of 2,3,4,5-tetrachlorophthalic acid anhydride (2.85 g, 10.0 mmol) and 3-amino-3-(4'-methoxyphenyl)propionic acid (1.95 g, 10.0 mmol) in 25 mL of acetic acid under nitrogen was heated to reflux for 4.5 hours. Solid formed as the reaction mixture cooled. The resulting slurry was filtered and the solid dried in vacuo (60°C, <2 mm) to afford 4.24 g (92%) of 3-(2,3,4,5-tetrachlorophthalimido)-3-(4'-methoxyphenyl)propionic acid as an off-white solid contaminated with ~1% acetic acid: mp 235.6-238°C; ¹H NMR (DMSO-d₆) δ 12.44 (br s, 1H, COOH), 7.36 (d, J = 8.7 Hz, 2 H), 6.90 (d, 1 H, J = 8.7 Hz), 5.64 (m, 1 H), 3.72 (s, 3 H), 3.35 (m, 2 H); ¹³C NMR (DMSO-d₆) δ 171.5, 163.0, 158.8, 138.4, 129.9, 128.6, 128.2, 127.6, 113.8, 55.0, 50.2, 35.6. Anal. Calcd for C₁₈H₁₁NO₅Cl₄. Theory: C, 46.68; H, 2.39; N, 3.02. Found: C, 46.58; H, 2.31; N, 2.91.

EXAMPLE 68

A stirred mixture of 4-nitrophthalic acid anhydride (1.93 g, 10.0 mmol) and 3-amino-3-(4'-methoxyphenyl)propionic acid (1.95 g, 10.0 mmol) in 20 mL of acetic acid under nitrogen was heated to reflux for 4.5 hours. The reaction mixture was concentrated to an oil which was stirred in 18 mL of ethyl acetate overnight. The resulting slurry was filtered and the solid air-dried and then dried in vacuo (70°C, < 2mm, 2 h) to afford 2.52 g (68%) of the product as a pale yellow powder contaminated with acetic acid and ethyl acetate. The material was dried in vacuo overnight at 90°C to afford a yellow glass which was slurried in 15 mL of ethyl acetate to afford after filtration and drying 1.72 g (46%) of 3-(4'-nitrophthalimido)-3-(4'-methoxyphenyl)propionic acid as a pale yellow powder contaminated with ethyl acetate: mp 90-91.5°C; ¹H NMR (DMSO-d₆) δ 8.75-8.60 (m, 1 H), 8.5 (m, 2 H), 8.12 (d, J = 8 Hz, 1 H), 7.38 (d, 2 H, J = 8.7 Hz H, Ar), 6.90 (d, 2 H, J = 8.7 Hz, Ar), 5.75-5.6 (m, 1 H, CHCO), 3.72 (s, 3 H, OMe), 3.47 (dd, 1 H, J = 8, 16.6 Hz), 3.33 (dd, 1 h, J = 7 Hz, 16.6 Hz); ¹³C NMR

(DMSO-d₆) δ 171.6, 165.9, 165.7, 158.8, 151.5, 135.6, 132.4, 130.3, 129.8, 128.5, 124.7, 118.0, 113.9, 55.0, 50.2, 35.8.. Anal. Calcd for C₁₈H₁₄N₂O₇-1/3 EtOAc. Theory: C, 58.09 ; H, 4.20; N, 7.01. Found: C, 57.89; H, 4.29; N, 6.83.

5

EXAMPLE 69

The procedure of Example 48 was followed utilizing 3-amino-3-(2'-naphthyl)propionic acid and N-carbethoxyphthalimide to afford 1.43 g (83%) of crude product as an off-white powder. The crude product was purified by flash chromatography (silica gel, 4-4.5% methanol/methylene chloride) to afford 1.11 g of product as a white foam. The foam was slurried in 15 mL of ethano to afford 1.03 g of 3-phthalimido-3-(2'-naphthyl)propionic acid as a white powder contaminated with ethanol and methylene chloride: ¹H NMR (DMSO-d₆) δ ; 12.56 (br s, 1H), 8.1-7.75 (m, 8H), 7.7-7.45 (m, 3 H), 5.89 (m, 1 H), 3.62 (dd, 1 H, J = 16.6, 9 Hz), 3.46 (dd, J = 16.6, 6.8 Hz); ¹³C NMR (DMSO-d₆) δ 171.8, 167.7, 136.3, 134.6, 132.6, 132.2, 131.1, 128.3, 127.9, 127.3, 126.3, 126.2, 125.6, 125.1, 123.2, 50.2, 35.8.

20

EXAMPLE 70

The procedure of Example 39 utilizing 3-phthalimido-3-(2'-naphthyl)propionic acid and carbonyldiimidazole to afford the crude product as a white powder. 3-Phthalimido-3-(2'-naphthyl)propionamide was recrystallized from 40 mL of ethyl acetate to afford 0.259 g (35%) of the product as fine white prisms: ¹H NMR (DMSO-d₆) δ 8.15-7.75 (m, 8 H, Ar), 7.75-7.4 (m, 4 h, Ar and CONH), 6.94 (br s, 1 H, CONH), 5.93 (overlapping dd, 1 H, CHN), 3.55-3.15 (m, 2 H, CH₂CO); ¹³C NMR (DMSO-d₆) δ 171.2, 167.7, 136.7, 134.5, 132.6, 132.2, 131.2, 128.1, 127.8, 127.3, 126.3, 126.1, 125.5, 125.2, 123.1, 50.4, 36.7. Anal. Calcd for C₂₁H₁₆N₂O₃. Theory: C, 73.24 ; H, 4.68; N, 8.13. Found: C, 73.07; H, 4.61; N, 7.91.

EXAMPLE 71

A stirred suspension of 3-amino-3-(3',4'-dimethoxyphenyl)propionic acid hydrochloride (0.689 g, 2.50 mmol) and 4-pyridylidicarboxylic acid anhydride (0.373 g, 2.50 mmol) in 20 mL of acetic acid was refluxed for overnight. The cooled reaction was filtered to remove a trace amount of solid and the filtrate concentrated to a thick yellow oil. The oil was diluted with 20 mL of ethyl acetate and heated to reflux and allowed to cool to room temperature. The resulting slurry was filtered and the filtrate concentrated to afford a yellow oil which was purified by flash chromatography (silica gel, 2/8 ethyl acetate/methylene chloride) to afford 0.592 g (64%) of methyl 3-(1,3-dioxo-5-azaisoindol-2-yl)-3-(3',4'-dimethoxyphenyl)-propionate as a yellow oil which slowly solidified to afford a very pale yellow solid: ^1H NMR (DMSO-d₆) δ 8.15-7.75 (m, 8 H, Ar), 7.75-7.4 (m, 4 h, Ar and CONH), 9.13 (s, 1 H, Ar), 9.11 (d, 1 H, J = 4.8 Hz), 7.90 (d, 1 H, J = 4.8 Hz), 7.03 (s, 1 H), 6.93 (m, 2 H), 5.67 (overlapping dd, 1 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.56 (s, 3 H), 3.65-3.30 (m, 2 H); ^{13}C NMR (DMSO-d₆) δ 170.7, 166.9, 166.5, 156.0, 148.6, 148.5, 144.1, 138.7, 130.4, 125.2, 119.1, 116.9, 111.6, 111.1, 55.4, 51.6, 50.1, 35.4..

EXAMPLE 72

To a stirred solution of 3-amino-3-(4'-benzyloxy-3'-methoxyphenyl)propionic acid (1.505 g, 5.00 mmol) and sodium carbonate (0.572 g, 5.40 mmol) in a mixture of 75 mL of water and 175 mL of acetonitrile (mixture was warmed gently to dissolve solid) was added N-carbethoxyphthalimide (1.096 g, 5.00 mmol). The mixture was stirred for 1 hour, then partially concentrated in vacuo to remove the acetonitrile. A small amount of solid formed which was removed by filtration. The pH of the solution was adjusted to 1 with 4 N Hydrochloric acid, a gum formed. To the stirred mixture was added 1 mL of ether and the mixture was then stirred overnight. The resulting slurry was filtered and the solid dried to afford 1.63 g

(75%) of 3-phthalimido-3-(4'-benzyloxy-3'-methoxyphenyl)-propionic acid as a white powder; ^1H NMR (DMSO-d₆) δ 12.43 (br s, 1 H, COOH), 8.0-7.8 (m, 4 H, Ar), 7.60-7.25 (m, 5 H), 7.15-6.85 (m, 3 H, Ar), 5.25 (dd, 1 H, J = 9, 6.6 Hz), 5.05 (s, 2 H, OCH₂), 3.76 (s, 3 H, OMe), 3.52 (dd, 1 H, J = 9, 16.5 Hz), 2.29 (dd, 1 H, J = 6.6, 16.5 Hz); ^{13}C NMR (DMSO-d₆) δ 171.7, 167.6, 148.9, 147.3, 137.0, 134.6, 131.7, 131.0, 128.3, 127.7, 127.6, 123.1, 119.1, 113.3, 111.3, 69.8, 55.5, 50.1, 36.0. Anal. Calcd for C₂₅H₂₁N₁O₆. Theory: C, 69.66; H, 4.91; N, 3.25. Found: C, 69.50; H, 4.85; N, 3.22.

EXAMPLE 73

A mixture of 3-phthalimido-3-(4'-benzyloxy-3'-methoxyphenyl)propionic acid (1.00 g, 2.32 mmol), carbonyldiimidazole (0.406 g, 2.50 mmol) and a catalytic amount of dimethylaminopyridine in 20 mL of dry tetrahydrofuran under nitrogen was stirred for 1 hour. To the reaction solution was then added 0.25 mL of concentrated ammonium hydroxide. After 15 minutes, the reaction mixture was concentrated in vacuo to an oil which was diluted with 20 mL of water and stirred overnight. The resulting slurry was filtered and the solid dried to afford 0.645 g (65%) of 3-phthalimido-3-(4'-benzyloxy-3'-methoxyphenyl)propionamide as a white powder: ^1H NMR (DMSO-d₆) δ 7.84 (m, 4 H, Ar), 7.60-7.25 (m, 5 H), 7.53 (br s, 1 H, CONH), 7.15-6.8 (m, 4 H), 5.67 (t, 1 H, J = 7.8 Hz), 5.04 (s, 2 H, OCH₂), 3.75 (s, 3 H, OMe), 3.19 (d, 2 H, J = 9, 16.5 Hz); ^{13}C NMR (DMSO-d₆) δ 171.1, 167.6, 148.8, 147.2, 137.0, 134.5, 132.0, 131.2, 128.3, 127.7, 127.6, 123.0, 119.3, 113.2, 111.4, 69.8, 55.5, 50.3, 36.9. Anal. Calcd for C₂₅H₂₂N₂O₅. Theory: C, 69.76; H, 5.15; N, 6.51. Found: C, 69.54; H, 5.13; N, 6.28.

EXAMPLE 74

To a stirred solution of 3-amino-3-(4'-butoxy-3'-methoxyphenyl)propionic acid (1.31 g, 4.98 mmol) and sodium carbonate (0.554 g, 5.23 mmol) in a mixture of 100 mL of water and 100 mL of acetonitrile (mixture was warmed gently to dissolve solid, small amount of brown solid did not dissolve removed by filtration) was added N-carbethoxyphthalimide (1.09 g, 4.98 mmol). The mixture was stirred for 1 hour, then partially concentrated in vacuo to remove the acetonitrile. The pH was adjusted to 0-1 with 4 N Hydrochloric acid. An oil formed, 3 mL of ether was added and the mixture stirred overnight. The oil did not solidify and was extracted in methylene chloride. The organic layer was dried (sodium sulfate) and concentrated to a yellow oil which was purified by flash chromatography (silica gel, 5/95 methanol/methylene chloride) to afford 1.02 g of 3-phthalimido-3-(4'-butoxy-3'-methoxyphenyl)propionic acid containing an unidentified impurity as a yellow oil which slowly crystallized: ^1H NMR (DMSO- d_6) δ 7.95-7.8 (m, 4 H, Ar), 7.03 (s, 1 H), 6.9 (m, 2 H), 5.61 (dd, 1 H, J = 9, 6.7 Hz), 3.91 (t, 2 H, J = 6.4 Hz), 3.74 (s, 3 H), 3.47 (dd, 1 H, J = 16.5, 6.7 Hz), 3.27 (dd, 1 H, J = 16.5, 6.7 Hz), 1.75-1.55 (m, 2 H) 1.5-1.3 (m, 2 H), 0.91 (t, 3 H, J = 7.3 Hz); ^{13}C NMR (DMSO- d_6) δ 171.8, 167.7, 148.8, 147.8, 134.6, 131.3, 131.1, 123.2, 119.3, 112.9, 111.4, 67.8, 55.5, 50.1, 30.8, 18.7, 13.6.

EXAMPLE 75

By following the procedure of Example 70 utilizing 3-phthalimido-3-(4'-butoxy-3'-methoxyphenyl)propionic acid and carbonyl diimidazole to afford 0.742 g (74%) of crude product as a pale yellow powder. The crude product was recrystallized from ethyl acetate (16 mL) to afford 0.517 (52%) of 3-phthalimido-3-(4'-butoxy-3'-methoxyphenyl)propionamide as fine fluffy white needles: HPLC 99.1%; ^1H NMR (DMSO- d_6) δ 7.95-7.75 (m, 4 H, Ar), 7.54 (br s, 1 H, CONH), 7.04 (s, 1 H, Ar), 7.0-6.75 (m, 2 H), 6.86 (br s, 1 H, CONH), 5.67 (t, 1 H, J = 8

Hz), 3.90 (t, 2 H, J = 6 Hz), 3.73 (s, 3 H), 3.20 (d, 1 H, J = 8 Hz, CH_2CO), 1.8-1.55 (m, 2 H) 1.5-1.3 (m, 2 H), 0.91 (t, 3 H, J = 7 Hz); ^{13}C NMR (DMSO- d_6) δ 171.2, 167.6, 148.8, 147.7, 134.5, 131.6, 131.2, 123.0, 119.4, 112.8, 111.4, 67.8, 55.5, 50.3, 36.9, 30.7, 18.6, 13.6.

EXAMPLE 76

A stirred mixture of tetrachlorophthalic anhydride (2.85 g, 10.0 mmol) and phenylglycine (10.0 mmol) in 20 mL of acetic acid under nitrogen was heated to reflux for 4 hours. The reaction solution was allowed to cool to room temperature with stirring. The resulting slurry was filtered and the solid dried to afford 3.58 g (85%) of 2-(3,4,5,6-tetrachlorophthalimido)-2-phenylacetic acid as a white powder: ^1H NMR (DMSO- d_6) δ 7.55-7.25 (m, 5 H, Ph), 6.06 (s, 1 H, CH); ^{13}C NMR (DMSO- d_6) δ 168.4, 162.5, 138.8, 134.2, 129.4, 128.6, 128.1, 128.1, 127.6, 55.7. Anal. Calcd for $\text{C}_{16}\text{H}_7\text{N}_1\text{O}_4\text{Cl}_4$. Theory: C, 45.68; H, 1.68; N, 3.34. Found: C, 45.78; H, 1.61; N, 3.29.

EXAMPLE 77

A mixture of 4,5-dichlorophthalic anhydride (2.17 g, 10.0 mmol) and D,L-phenylglycine (Aldrich, 95%) (1.59g, 10.0mmol) in 20 mL of acetic acid was refluxed for 6 h under nitrogen. The reaction mixture was allowed to cool. The slurry was filtered and the solid was dried to afford 2.86g (82%) of 2-(4',5'-dichlorophthalimido)-2-phenylacetic acid as a white powder: mp 228-232°C; ^1H NMR (DMSO- d_6 , 250 MHz) δ : 8.25 (s, 8 H), 7.52-7.30 (m, 5 H), 6.04 (s, 1H); ^{13}C NMR (DMSO- d_6) δ 168.7, 165.2, 138.0, 134.6, 130.9, 129.3, 128.1, 128.1, 125.8, 55.5. Anal. Calcd for $\text{C}_{16}\text{H}_9\text{N}_1\text{O}_4\text{Cl}_2$. Theoretical: C, 54.88; H, 2.59; N, 4.00. Found: C, 54.93; H, 2.54; N, 3.95.

EXAMPLE 78

5 A slurry of 3-nitrophthalic anhydride (1.93g, 10.0 mmol) and D,L-phenylglycine (Aldrich, 95%) (1.59g, 10.0mmol) in 20 mL of acetic acid was refluxed for 5 h under nitrogen. The mixture was cooled, the slurry filtered and the solid dried to afford 2.32g (72%) of 2-phenyl-2-(3'-nitrophthalimido)acetic acid as a white powder. mp 213-229°C; ¹H NMR (DMSO-d₆, 250 MHz) δ 8.40-8.02 (m, 3H), 7.55-7.26 (m, 5 H), 6.08 (s, 1H); ¹³C NMR (DMSO-d₆) δ 168.6, 165.1, 162.4, 144.5, 136.8, 134.4, 10 132.8, 129.4, 129.0, 128.1, 128.1, 127.5, 122.5, 55.6. Anal. Calcd for C₁₆H₁₀N₂O₄. Theoretical: C, 65.31; H, 3.43; N, 9.52. Found: C, 58.89; H, 3.11; N, 8.52.

EXAMPLE 79

15 A mixture of 3-nitrophthalic anhydride (1.54, 8.0 mmol) and 3-amino-3-(4'-methoxy) phenyl propionic acid (1.56g, 8.0mmol) in 15 mL of acetic acid was refluxed for 3.5 h under nitrogen. The reaction was cooled and removed some of the solvent. The slurry was filtered and the solid was dried to afford 2.34g (79%) of 3-(4'-methoxyphenyl)-3-(3'-nitro- 20 phthalimido)propionic acid as a white powder: mp 178-180°C; ¹H NMR (DMSO-d₆, 250 MHz) δ 8.07-8.02 (m, 3 H), 7.38 (d, 2 H, J = 8.7), 6.90 (d, 2H, J = 8.7, 5.68-5.07 (m, 1H), 3.72 (s, 3H), 3.48-3.22 (m, 2H); ¹³C NMR (DMSO-d₆) δ 171.6, 165.7, 163.0, 158.8, 144.4, 136.4, 133.0, 130.2, 128.6, 128.5, 127.0, 122.4, 25 113.9, 55.1, 50.0, 35.8. Anal. Calcd for C₁₈H₁₄N₂O₇. Theoretical: C, 58.38; H, 3.81; N, 7.56. Found: C, 58.18; H, 3.79; N, 7.36.

EXAMPLE 80

30 A mixture of 4,5-dichlorophthalic anhydride (0.91, 4.19 mmol) and 3-amino-3-(4'-methoxy) phenyl propionic acid in 10mL acetic acid was stirred under nitrogen for 6 hours. The reaction was cooled and removed some of the solvent. The slurry was filtered and the solid was dried to afford 1.20g (61%) of

3-(4',5'-dichlorophthalimido)-3-(4'-methoxyphenyl)propionic acid as a white powder. mp 182-185°C; ^1H NMR (DMSO-d₆, 250 MHz) δ 8.19 (s, 2H), 7.34 (d, 2 H, J = 8.7), 6.90 (d, 2H, J = 8.7), 5.61 (t, 1H, J = 7.8), 3.72 (s, 3H), 3.50-3.20 (m, 2H). ^{13}C NMR (DMSO-d₆) δ 171.6, 165.8, 158.8, 137.6, 131.0, 130.4, 128.4, 125.4, 113.9, 55.1, 50.0, 35.8. Anal. Calcd for C₁₈H₁₄N₂O₇. Theoretical: pending

EXAMPLE 81

A mixture of 3-phthalimido-3-(3',4'-dimethoxyphenyl)propionic acid (0.86 g, 2.41 mmol) and carbonyldiimidazole (0.43 g, 2.65 mmol) with trace amount of 4-dimethylaminopyridine in 10 mL of tetrahydrofuran under nitrogen was stirred for 30 min at room temperature, then 0.23 mL (2.41 mmol) of 3-pyridyl-carbinol was added to the above solution. After 1 hour, the reaction mixture was concentrated to an oil. The oil was dissolved in 25 mL of ethylacetate and the mixture was extracted with water (3x25 mL). The organic layer was dried over sodium sulfate and to afford the crude product as a light yellow. The crude product was then purified by flash chromatography (silica gel, MeOH/CH₂Cl₂, 0-2%, (v/v)) to afford 0.54 g (50%) of 3-Pyridinemethyl 3-phthalimido-3-(3',4'-dimethoxyphenyl)-propionate as a light yellow foam: ^1H NMR (dmso-d₆, 250 MHz) δ 8.4-8.5 (m, 2 H), 7.84 (s, 4 H, Ar), 7.5-7.6 (m, 1 H), 7.2-7.3 (m, 1 H), 6.7-7.1 (m, 3 H, Ar), 5.65 (dd, 1 H, J₁ = 6 Hz, J₂ = 9.6 Hz), 5.09 (s, 2 H), 3.74 (s, 6 H), 3.4-3.7 (m, 2 H); ^{13}C NMR (dmso-d₆) δ 170.1, 167.6, 149.2, 148.6, 148.4, 135.7, 134.7, 131.4, 131.0, 130.8, 123.3, 123.2, 119.3, 111.7, 111.0, 63.4, 55.5, 55.4, 49.9, 35.9. Anal. Calcd for C₂₅H₂₂N₂O₆. Theoretical C, 67.26; H, 4.97; N, 6.27. Found C, 67.06; H, 4.99; N, 6.20.

EXAMPLE 82

A mixture of 3-phthalimido-3-(3',4'-dimethoxyphenyl)propionic acid (0.60 g, 1.69 mmol), carbonyldiimidazole (0.28 g, 1.77 mmol) and trace amount of 4-dimethylaminopyridine in 10 mL of tetrahydrofuran was stirred at room temperature under nitrogen for 30 min. To the reaction mixture was added 3-aminomethylpyridine (0.18 mL, 1.77 mmol). The reaction mixture was stirred for 20 min, then 10 mL of water was added and the tetrahydrofuran was removed under reduced pressure. The resulting slurry was filtered, the solid was washed with water, and dried in vacuo (60 °C, <1 mm) to afford 0.57 g (76%) of N-3-Methylpyridyl 3-phthalimido-3-(3',4'-dimethoxyphenyl)propionamide as a white powder: mp 171.2-172.4 °C; ¹H NMR (dmso-d₆, 250 MHz) δ 8.69 (t, 1 H, J = 6 Hz), 8.36 (m, 2H), 7.85 (s, 4 H, Ar), 6.8-7.4 (m, 5 H), 5.71 (t, 1 H, J = 8 Hz), 4.22 (d, 2 H, J = 5.2 Hz), 3.73 (s, 3 H), 3.71 (s, 3 H), 3.31 (d, 2 H, J = 8 Hz); ¹³C NMR (dmso-d₆) δ 169.4, 167.7, 148.5, 148.3, 147.9, 134.7, 134.6, 134.5, 131.4, 131.2, 123.1, 119.5, 111.6, 111.2, 55.5, 55.4, 50.6, 39.6, 37.4. Anal. Calcd for C₂₅H₂₃N₃O₅. Theoretical C, 67.41; H, 5.20; N, 9.43. Found C, 67.35; H, 5.14; N, 9.34.

EXAMPLE 83

To a stirred solution of 3-phthalimido-3-(3',4'-dichlorophenyl)propionic acid (1.10 g, 3.02 mmol) in 20 mL of tetrahydrofuran at room temperature under nitrogen was added carbonyldiimidazole (0.51 g, 3.17 mmol) and a catalytic amount of 4-dimethylaminopyridine. The mixture was stirred for 45 min and then concentrated ammonium hydroxide (0.21 mL, 3.2 mmol) was added. The reaction mixture was stirred for 10 minutes and then the tetrahydrofuran was removed under reduced pressure. To the resulting mixture was added 20 mL of water, a light yellow oil was formed. To the mixture was added 3 mL of ether, the mixture was stirred at room temperature for 1 hour. The resulting slurry was filtered, the solid was washed with water and air-dried to afford 0.73 g of the crude product as a

white solid. The crude product was purified by flash chromatography (silica gel, hexane/CH₂Cl₂, 22-0% (v/v)) to afford 0.39 g (36%) of 3-Phthalimido-3-(3',4'-dichlorophenyl)-propionamide as a white powder: ¹H NMR (dmso-d₆, 250 MHz) δ 5
5 7.83 (m, 4 H, Ar), 7.35-7.75 (m, 4 H), 6.93 (br s, 1 H), 5.72 (t, 1 H, J = 8 Hz), 3.25 (dd, 1 H, J₁ = 8 Hz, J₂ = 15 Hz), 3.14 (dd, 1 H, J₁ = 8 Hz, J₂ = 15 Hz); ¹³C NMR (dmso-d₆) δ 170.8, 167.6, 140.2, 134.6, 131.2, 131.0, 130.7, 130.3, 129.2, 127.7, 123.2, 49.3, 36.5. Anal. Calcd for C₁₇H₁₂N₂O₃Cl₂.
10 Theoretical C, 54.69; H, 3.54; N, 7.53. Found C, 54.69; H, 3.38; N, 7.15.

EXAMPLE 84

To 150 mL of stirred methanol at 0 °C under nitrogen was slowly added thionyl chloride (14.2 mL, 194.4 mmol). To the 15 reaction mixture was then added 3-amino-3-(3',4'-dimethoxyphenyl)propionic acid (15.5 g, 64.8 mmol). The reaction mixture was stirred at 0 °C for 30 minutes and then allowed to warm to room temperature, and stirred overnight. The reaction solution was concentrated to an oil and then 20 diluted with 200 mL of CH₃OH/Et₂O (1/3) and stirred. The resulting slurry was filtered and the solid was washed with a copious amount of ether. The solid was dried in vacuo (60 °C, < 1 mm) to afford 1.83 g (66%) of Methyl 3-amino-3-(3',4'-dimethoxyphenyl)propionate hydrochloride as a white powder: ¹H NMR (dmso-d₆, 250 MHz) δ 8.59 (br s, 3 H, NH₃), 6.9-7.3 (m, 3 H, Ar), 4.52 (overlapping dd, 1 H), 3.77 (s, 3 H, OCH₃), 3.75 (s, 3 H, OCH₃), 3.57 (s, 3 H, OCH₃), 3.16 (dd, 1 H, J₁ = 6 Hz, J₂ = 16 Hz), 2.98 (dd, 1 H, J₁ = 8 Hz, J₂ = 16 Hz); ¹³C NMR (dmso-d₆) δ 169.6, 149.0, 129.0, 120.0, 111.5, 111.4, 25 55.7, 55.5, 51.7, 50.8, 38.5. Anal. Calcd for C₁₂H₁₈NO₄Cl. Theoretical C, 52.27; H, 6.58; N, 5.08. Found C, 52.44; H, 6.53; N, 5.01.

EXAMPLE 85

A mixture of methyl 3-amino-3-(3',4'-dimethoxyphenyl)propionate hydrochloride (1.38 g, 5.00 mmol), sodium carbonate (0.53 g, 5.00 mmol), and N-carboethoxyphthalimide (1.10 g, 5.0 mmol) in 40 mL of $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (1/1) was stirred for 1 hour at room temperature. The reaction solution was then partially concentrated under reduced pressure to remove the acetonitrile. This afforded a white gum in water. To the mixture was then added 5 mL of ether and the mixture was stirred for 2 hours. The resulting slurry was filtered, the solid was washed with a copious amount of water and air-dried overnight to afford 1.69 g (92%) of Methyl 3-phthalimido-3-(3',4'-dimethoxyphenyl)propionate as a white solid: mp 114.1-115.6. ^1H NMR (dmso- d_6 , 250 MHz) δ 7.80-7.95 (m, 4 H, Ar), 6.80-7.10 (m, 3 H, Ar), 5.65 (dd, 1 H, J_1 = 7 Hz, J_2 = 9 Hz), 3.74 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 3.55 (s, 3 H, OCH_3), 3.30-3.67 (m, 2 H); ^{13}C NMR (dmso- d_6) δ 170.8, 167.6, 148.6, 148.4, 134.7, 131.1, 131.0, 123.2, 119.3, 111.7, 111.0, 55.5, 51.6, 49.9, 35.6. Anal. Calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_6$. Theoretical C, 65.03; H, 5.18; N, 3.79. Found C, 65.17; H, 5.14; N, 3.75. HPLC 99%.

EXAMPLE 86

To a stirred solution of benzaldehyde (1.58 mL, 15.5 mmol) in 10 mL of absolute ethanol at room temperature under nitrogen was added (R)- α -methylbenzylamine (2.0 mL, 15.51 mmol, 99% ee.). The reaction mixture was stirred for 3 hours. The reaction solution was then dried over magnesium sulfate and diluted to a 60 mL volume with EtOH. Ethanol washed Raney-Ni (~ 1.5 g) was added and the resulting suspension was treated with 58 psi of H₂ in a Parr Type Shaker. After 1 day, additional Raney-Ni (~ 1 g) and 30 mL of ethanol were added and the hydrogenolysis continued for 3 days. The reaction mixture was filtered through Celite to remove the catalyst and concentrated to afford 3.11 g (95%) of N-Benzyl (R)- α -methylbenzylamine as a pale yellow oil contaminated with ~ 5% of benzyl alcohol and (R)- α -methylbenzylamine; ¹H NMR (dmso-d₆, 250 MHz) δ 7.1-7.5 (m, 10 H, Ar), 3.68 (q, 1 H, J = 6.6 Hz), 3.48 (dd, 2 H, J₁ = 13.6 Hz, J₂ = 20.5 Hz), 1.26 (d, 3 H, J = 6.6 Hz, CH₃); ¹³C NMR (dmso-d₆) δ 146.1, 141.0, 128.2, 128.0, 127.8, 126.5, 126.4, 56.7, 50.6, 24.5. This mixture was used directly in the next reaction.

EXAMPLE 87

To stirred solution of N-benzyl (R)- α -methylbenzylamine (1.9 g, 9.0 mmol) in 50 mL of tetrahydrofuran at 0 °C under nitrogen was added n-butyl lithium (1.6 M in hexanes; 9.0 mmol). The resulting red solution was stirred at 0 °C for 15 min and then cooled to -78 °C. To the reaction mixture was then dropwise added methyl *trans*-3-(3',4'-dimethoxyphenyl)-propion-2-enate (1.33 g, 6.0 mmol) in 20 mL tetrahydrofuran and the mixture was stirred for 15 min at -78 °C to afford a yellow solution. The reaction was then quenched by the addition of saturated ammonium chloride (20 mL). The mixture was allowed to warm to room temperature and poured into 40 mL of saturated sodium chloride (aq). The mixture was extracted with ether (2x 60 mL) and the combined organic layers dried (MgSO₄) and concentrated to afford 3.35 g of crude product as

a yellow oil. The oil was purified by flash chromatography (silica gel, hexane/CH₂Cl₂, 30-0%, (v/v)) to afford 1.24 g (48%) of Methyl (S)-N-Benzyl-N-(R)-a-methylbenzyl-3-(3',4'-dimethoxyphenyl)propionate adduct as colorless oil: ¹H NMR (dmso-d₆, 250 MHz) δ 6.7-7.5 (m, 13 H, Ar), 3.9-4.2 (m, 2 H), 3.78 (s, 3 H, OCH₃), 3.73 (s, 3 H, OCH₃), 3.65 (s, 2 H), 3.43 (s, 3 H, OCH₃), 2.6-2.9 (m, 2 H), 1.03 (d, 3 H, J = 7 Hz); ¹³C NMR (dmso-d₆) δ 171.6, 148.3, 147.8, 144.6, 141.5, 133.6, 128.1, 128.0, 127.7, 127.5, 126.7, 126.4, 119.6, 111.9, 111.2, 58.2, 56.4, 55.4, 55.3, 51.1, 49.7, 35.6, 17.1.

EXAMPLE 88

Debenzylation of the above pure adduct was done following the literature procedure S. G. Davies and O. Ichihara (Tetrahedron Asymmetry 1991, 2, 183.). To a stirred solution 15 methyl (S)-3-(N-benzyl-N-(R)-a-methylbenzylamino)-3-(3',4'-dimethoxyphenyl)propionate (1.20 g, 2.77 mmol) in a mixture of MeOH (20 mL), water (2 mL) and acetic acid (0.5 mL) was added 20% palladium hydroxide on charcoal. The reaction mixture was 20 treated with hydrogen (54 psi) at room temperature for 23 h on a Parr Type Shaker. The reaction mixture was filtered through Celite and then concentrated to afford the product as an acetate salt. The salt was dissolved in 10 mL of water, stirred with 0.7 mL 4 N HCl and then concentrated to a white solid. 25 The solid was diluted with 40 mL of ether and stirred for 20 min. The slurry was filtered and the solid was dried in vacuo (room temperature, < 1 mm) to afford 0.57 g (75%) of Methyl (S)-3-amino-3-(3',4'-dimethoxyphenyl)propionate hydrochloride as a white solid: HPLC 96% ee (Chiral Crownpack CR+ column); 30 ¹H NMR (dmso-d₆, 250 MHz) δ 8.73 (br s, 3 H, NH₃), 6.90-7.40 (m, 3 H, Ar), 4.51 (dd, 1 H, J₁ = 6 Hz, J₂ = 8 Hz), 3.77 (s, 3 H, OCH₃), 3.75 (s, 3 H, OCH₃), 3.56 (s, 3 H, OCH₃), 3.2 (dd, 1 H, J₁ = 6 Hz, J₂ = 16 Hz), 3.0 (dd, 1 H, J₁ = 8 Hz, J₂ = 16 Hz); ¹³C NMR (dmso-d₆) δ 169.6, 149.0, 148.7, 129.0, 120.0, 35 111.5, 111.4, 55.7, 55.5, 51.7, 50.8, 38.6. Anal. Calcd for

$C_{12}H_{18}NO_4Cl \cdot 0.48 H_2O$. Theoretical C, 50.67; H, 6.72; N, 4.92. Found C, 50.67; H, 6.46; N, 4.83.

EXAMPLE 89

Prepared as described earlier as methyl 3-phthalimido-3-(3',4'-dimethoxyphenyl)propionate from methyl (S)-3-amino-3-(3',4'-dimethoxyphenyl)propionate (0.45 g, 1.63 mmol), sodium carbonate (0.17 g, 1.63 mmol) and N-carboethoxyphthalimide (0.36 g, 1.63 mmol). Methyl (S)-3-phthalimido-3-(3',4'-dimethoxyphenyl)propionate was obtained as a white powder, 0.51 g (85%); 1H NMR (dmso-d₆, 250 MHz) δ 7.87 (br s, 4 H, Ar), 6.80-7.10 (m, 3 H, Ar), 5.65 (dd, 1 H, J_1 = 7 Hz, J_2 = 9 Hz), 3.73 (s, 3 H, OCH₃), 3.72 (s, 3 H, OCH₃), 3.55 (s, 3 H, OCH₃), 3.30-3.67 (m, 2 H); ^{13}C NMR (dmso-d₆) δ 170.8, 167.7, 148.6, 148.4, 134.7, 131.1, 131.0, 123.2, 119.3, 111.7, 111.0, 55.5, 51.6, 49.9, 35.6. Anal. Calcd for C₂₀H₁₉NO₆. Theoretical C, 65.03; H, 5.18; N, 3.79. Found C, 64.94; H, 5.29; N, 3.86. HPLC 97%.

EXAMPLE 90

Prepared as described earlier for N-benzyl-(R)-a-methylbenzylamine from benzaldehyde (3.94 mL, 38.8 mmol) and (S)-a-methylbenzylamine (5.0 mL, 38.8 mmol, 96% ee.) to afford 7.88 g (96%) of N-Benzyl-(S)-a-methylbenzylamine as an oil contaminated with 5% of benzyl alcohol and (S)-a-methylbenzylamine: 1H NMR (dmso-d₆, 250 MHz) δ 7.15-7.45 (m, 10 H, Ar), 3.69 (q, 1 H, J = 6.5 Hz), 3.48 (dd, 2 H, J_1 = 13.6 Hz, J_2 = 20.9 Hz), 2.45 (br s, 1 H, NH), 1.26 (d, 3 H, J = 6.5 Hz, CH₃); ^{13}C NMR (dmso-d₆) δ 146.0, 141.0, 128.1, 128.0, 127.8, 126.4, 126.3, 56.7, 50.6, 24.5. This mixture was directly used in the next reaction.

EXAMPLE 91

Prepared as described earlier as methyl (S)-3-(N-benzyl-N-(R)-a-methylbenzyl)-3-(3',4'-dimethoxyphenyl)propionate from butyl lithium (1.6 M in hexanes; 8.44 mmol), N-benzyl-(S)-a-methylbenzylamine (1.78 g, 8.44 mmol) and 3-(3',4'-dimethoxyphenyl)propyl-2-enate (1.50 g, 6.75 mmol) to afford 3.7 g of the crude product as a yellow oil. The oil was purified by flash chromatography (silica gel, ether/hexane, 20/80) to afford 0.57 g (20%) of Methyl (R)-3-(N-benzyl-N-(S)-a-methylbenzylamino)-3-(3',4'-dimethoxyphenyl)propionate as a colorless oil; ^1H NMR (dmso-d₆, 250 MHz) δ 6.80-7.50 (m, 13 H, Ar), 4.15 (dd, 1 H, J_1 = 6 Hz, J_2 = 9 Hz), 4.04 (q, 1 H, J = 7 Hz), 3.78 (s, 3 H, OCH₃), 3.73 (s, 3 H, OCH₃), 3.69 (s, 2 H), 3.43 (s, 3 H, OCH₃), 2.87 (dd, 1 H, J_1 = 6 Hz, J_2 = 15 Hz), 2.67 (dd, 1 H, J_1 = 9 Hz, J_2 = 15 Hz), 1.04 (d, 3 H, J = 7 Hz, CH₃); ^{13}C NMR (dmso-d₆) δ 171.6, 148.4, 147.8, 144.7, 141.5, 133.6, 128.1, 128.0, 127.8, 127.5, 126.7, 126.4, 119.6, 111.9, 111.2, 58.2, 56.4, 55.3, 51.1, 49.7, 35.6, 17.1.

EXAMPLE 92

Debenzylation of the above adduct was done following the literature procedure of S. G. Davies and O. Ichihara (Tetrahedron Asymmetry 1991, 2, 183.). A solution of methyl (R)-3-(N-benzyl-N-(S)-a-methylbenzylamino)-3-(3',4'-dimethoxyphenyl)propionate (0.57 g, 1.3 mmol) in MeOH (10 mL), water (1 mL) and acetic acid (0.25 mL) in the presence of 20% palladium hydroxide on charcoal was treated with hydrogen (59 psi) at room temperature for 23 h in a Parr Type Shaker. The mixture was filtered through Celite and then concentrated to afford the primary amine in an acetate salt, which was dissolved in 10 mL of water, stirred with 0.32 mL (4 N) HCl and concentrated to a white solid. To the solid was added 10 mL of ether and the mixture stirred for 30 min. The slurry was filtered, the solid was dried in vacuo (room temperature, < 1 mm) to afford 0.32 g (90%) of Methyl (R)-3-amino-3-(3',4'-dimethoxyphenyl)propionate hydrochloride as a white powder:

Chiral HPLC (Crownpak Cr+ Column 92% ee; ^1H NMR (dmso-d₆, 250 MHz) δ 8.61 (br s, 3 H, NH₃), 6.90-7.30 (m, 3 H, Ar), 4.53 (br s, 1 H), 3.77 (s, 3 H, OCH₃), 3.75 (s, 3 H, OCH₃), 3.57 (s, 3 H, OCH₃), 3.16 (dd, 1 H, J₁ = 6 Hz, J₂ = 16 Hz), 2.98 (dd, 1 H, J₁ = 8 Hz, J₂ = 16 Hz); ^{13}C NMR (dmso-d₆) δ 169.5, 149.0, 148.6, 128.9, 119.8, 111.4, 111.2, 55.6, 55.4, 51.7, 50.7, 38.4. Anal. Calcd for C₁₂H₁₈NO₄Cl @0.48 H₂O. Theoretical C, 50.67; H, 6.72; N, 4.92. Found C, 50.66; H, 6.54; N, 4.81.

EXAMPLE 93

Prepared as described earlier as methyl 3-phthalimido-3-(3',4'-dimethoxyphenyl)propionate from methyl (3R)-3-amino-3-(3',4'-dimethoxyphenyl)propionate (0.25 g, 0.91 mmol), sodium carbonate (0.10 g, 0.91 mmol) and N-carboethoxyphthalimide (0.20 g, 0.91 mmol). Methyl (3R)-3-phthalimido-3-(3',4'-dimethoxyphenyl)propionate was obtained as a white powder, 0.29 g (88%); ^1H NMR (dmso-d₆, 250 MHz) δ 7.87 (br s, 4 H, Ar), 6.80-7.10 (m, 3 H, Ar), 5.64 (dd, 1 H, J₁ = 7 Hz, J₂ = 9 Hz), 3.73 (s, 3 H, OCH₃), 3.72 (s, 3 H, OCH₃), 3.55 (s, 3 H, OCH₃), 3.30-3.67 (m, 2 H); ^{13}C NMR (dmso-d₆) δ 170.8, 167.6, 148.6, 148.4, 134.7, 131.1, 131.0, 123.2, 119.2, 111.7, 111.0, 55.5, 51.6, 49.9, 35.6. Anal. Calcd for C₂₀H₁₉NO₆ @0.80 H₂O. Theoretical C, 62.60; H, 4.99; N, 3.69. Found C, 62.60; H, 4.93; N, 3.69. HPLC 99.9%.

EXAMPLE 94

Tablets, each containing 50 mg of active imide ingredient, can be prepared in the following manner:

Constituents (for 1000 tablets)

active imide ingredient	50.0 g
lactose	50.7 g
wheat starch	7.5 g
polyethylene glycol 6000	5.0 g
talc	5.0 g
magnesium stearate	1.8 g
demineralized water	q.s.

The solid ingredients are first forced through a sieve of 0.6 mm mesh width. The active imide ingredient, the lactose, the talc, the magnesium stearate and half of the starch then are mixed. The other half of the starch is suspended in 40 mL of water and this suspension is added to a boiling solution of the polyethylene glycol in 100 mL of water. The resulting paste is added to the pulverulent substances and the mixture is granulated, if necessary with the addition of water. The granulate is dried overnight at 35°C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 6 mm diameter which are concave on both sides.

EXAMPLE 95

Tablets, each containing 100 mg of active imide ingredient, can be prepared in the following manner:

15 Constituents (for 1000 tablets)

active imide ingredient	100.0 g
lactose	100.0 g
wheat starch	47.0 g
20 magnesium stearate	3.0 g

All the solid ingredients are first forced through a sieve of 0.6 mm mesh width. The active imide ingredient, the lactose, the magnesium stearate and half of the starch then are mixed. The other half of the starch is suspended in 40 mL of water and this suspension is added to 100 mL of boiling water. The resulting paste is added to the pulverulent substances and the mixture is granulated, if necessary with the addition of water. The granulate is dried overnight at 35°C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 6 mm diameter which are concave on both sides.

EXAMPLE 96

Tablets for chewing, each containing 75 mg of active imide ingredient, can be prepared in the following manner:

<u>Composition</u> (for 1000 tablets)	
5	active imide ingredient 75.0 g
	mannitol 230.0 g
	lactose 150.0 g
	talc 21.0 g
10	glycine 12.5 g
	stearic acid 10.0 g
	saccharin 1.5 g
	5% gelatin solution q.s.

15 All the solid ingredients are first forced through a sieve of 0.25 mm mesh width. The mannitol and the lactose are mixed, granulated with the addition of gelatin solution, forced through a sieve of 2 mm mesh width, dried at 50°C and again forced through a sieve of 1.7 mm mesh width. The active imide ingredient, the glycine and the saccharin are carefully 20 mixed, the mannitol, the lactose granulate, the stearic acid and the talc are added and the whole is mixed thoroughly and compressed to form tablets of approximately 10 mm diameter which are concave on both sides and have a breaking groove on the upper side.

25

EXAMPLE 97

Tablets, each containing 10 mg of active imide ingredient, can be prepared in the following manner:

<u>Composition</u> (for 1000 tablets)	
30	active imide ingredient 10.0 g
	lactose 328.5 g
	corn starch 17.5 g
	Polyethylene glycol 6000 5.0 g
	talc 25.0 g
35	magnesium stearate 4.0 g
	demineralized water q.s.

40 The solid ingredients are first forced through a sieve of 0.6 mm mesh width. Then the active imide ingredient, lactose, talc, magnesium stearate and half of the starch are intimately

mixed. The other half of the starch is suspended in 65 mL of water and this suspension is added to a boiling solution of the polyethylene glycol in 260 mL of water. The resulting paste is added to the pulverulent substances, and the whole is 5 mixed and granulated, if necessary with the addition of water. The granulate is dried overnight at 35°C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 10 mm diameter which are concave on both sides and have a breaking notch on the upper side.

10

EXAMPLE 98

Gelatin dry-filled capsules, each containing 100 mg of active imide ingredient, can be prepared in the following manner:

15

Composition (for 1000 capsules)

active imide ingredient	100.0 g
microcrystalline cellulose	30.0 g
sodium lauryl sulphate	2.0 g
magnesium stearate	8.0 g

20

The sodium lauryl sulphate is sieved into the active imide ingredient through a sieve of 0.2 mm mesh width and the two components are intimately mixed for 10 minutes. The microcrystalline cellulose is then added through a sieve of 0.9 mm mesh width and the whole is again intimately mixed for 25 10 minutes. Finally, the magnesium stearate is added through a sieve of 0.8 mm width and, after mixing for a further 3 minutes, the mixture is introduced in portions of 140 mg each into size 0 (elongated) gelatin dry-fill capsules.

EXAMPLE 99

A 0.2% injection or infusion solution can be prepared, for example, in the following manner:

5	active imide ingredient	5.0 g
	sodium chloride	22.5 g
	phosphate buffer pH 7.4	300.0 g
	demineralized water	to 2500.0 mL

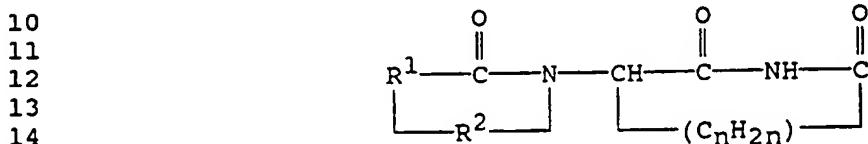
10 The active imide ingredient is dissolved in 1000 mL of water and filtered through a microfilter. The buffer solution is added and the whole is made up to 2500 mL with water. To prepare dosage unit forms, portions of 1.0 or 2.5 mL each are introduced into glass ampoules (each containing respectively 2.0 or 5.0 mg of imide).

1

2 WHAT IS CLAIMED IS:

3 1. In the process of preparing thalidomide in which N-phthaloylglutamine or N-phthaloylisoglutamine is cyclized with
 4 N,N'-carbonyldiimidazole, the improvement which comprises
 5 heating said N-phthaloylglutamine or N-phthaloylisoglutamine and N,N'-carbonyldiimidazole in refluxing
 6 anhydrous tetrahydrofuran.

7 2. A compound of the formula:



16 in which

17 R¹ is the divalent residue of (i) 3,4-pyridine, (ii) pyrrolidine, (iii) imidazole, (iv) naphthalene, (v) thiophene, or (vi) a straight or branched alkane of 2 to 6 carbon atoms, unsubstituted or substituted with phenyl or phenyl substituted with nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, wherein the divalent bonds of said residue are on vicinal ring carbon atoms;

26 R² is -CO- or -SO₂-; and

27 n has a value of 1, 2, or 3.

28 3. The compound of claim 2 wherein R¹ is a divalent residue of pyridine and R² is -CO-.

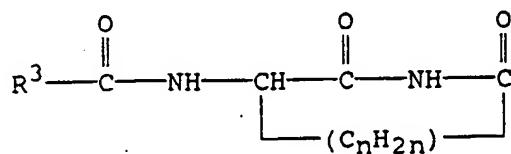
30 4. The compound of claim 2 wherein R¹ is a divalent residue of naphthalene and R² is -CO-.

32 5. The compound of claim 2 wherein R¹ is a divalent residue of imidazole and R² is -CO-.

34 6. The compound according to claim 2 which is 2-(2,6-dioxo-3-piperidinyl)-4-azaisoindoline-1,3-dione.

- 1 7. The compound according to claim 2 which is 2-(2,6-dioxo-3-
- 2 piperidinyl)-benzo[e]isoindoline-1,3-dione.
- 3 8. The compound according to claim 2 which is 5-(2,6-dioxo-3-
- 4 piperidinyl)-pyrrolo[3,4-d]imidazole-4,6-dione.
- 5 9. The method of reducing levels of TNF_α in a mammal which
- 6 comprises administering thereto an effective amount of a
- 7 compound according to claim 2.

- 8 10. A compound of the formula:



15 in which

16 R^3 is (i) phenyl substituted with 1 to 3 substituents each
17 selected independently from nitro, cyano, trifluoromethyl,
18 carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamyl,
19 acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon
20 atoms, alkoxy of 1 to 4 carbon atoms, or halo, (ii)
21 pyridyl, (iii) pyrrolyl, (iv) imidazolyl, (v) naphthyl,
22 (vi) thienyl, (vii) quinolyl, (viii) furyl, or
23 (ix) indolyl; and
24 n has a value of 1, 2, or 3.

- 25 11. The compound of claim 10 wherein R^3 is pyridyl.
- 26 12. The compound of claim 10 wherein R^3 is trifluoromethyl-
27 phenyl.
- 28 13. The compound of claim 10 wherein R^3 is cyanophenyl.
- 29 14. The compound of claim 10 wherein R^3 is methoxyphenyl.
- 30 15. The compound of claim 10 wherein R^3 is furyl.
- 31 16. The compound according to claim 10 which is 3-(trifluoro-
32 methylphenylcarboxamido)piperidine-2,6-dione.

1 17. The compound according to claim 10 which is 3-(cyanophen-
2 ylcarboxamido)piperidine-2,6-dione.

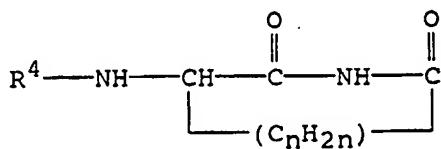
3 18. The compound according to claim 10 which is 3-(methoxy-
4 phenylcarboxamido)piperidine-2,6-dione.

5 19. The compound according to claim 10 which is 3-(3-pyridyl-
6 carboxamido)piperidine-2,6-dione.

7 20. The compound according to claim 10 which is 3-(2-furyl-
8 carboxamido)piperidine-2,6-dione.

9 21. The method of reducing levels of TNF_α in a mammal which
10 comprises administering thereto an effective amount of a
11 compound according to claim 10.

12 22. A compound of the formula:



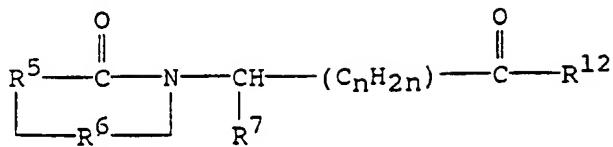
19 in which R^4 is alanyl, arginyl, glycyl, phenylglycyl, his-
20 tidyl, leucyl, isoleucyl, lysyl, methionyl, prolyl, sarco-
21 syl, seryl, homoseryl, threonyl, thronyl, tyrosyl, valyl,
22 benzimidol-2-yl, benzoxazol-2-yl, phenylsulfonyl,
23 methylphenylsulfonyl, or phenylcarbamoyl, and n has a value
24 of 1, 2, or 3.

25 23. The compound according to claim 22 which is 3-phenyl-
26 sulfonamidopiperidine-2,6-dione.

27 24. The compound according to claim 22 which is 3-(2-amino-3-
28 phenylpropaneamido)-piperidine-2,6-dione.

29 25. The method of reducing levels of TNF_α in a mammal which
30 comprises administering thereto an effective amount of a
31 compound according to claim 22.

1 26. A compound of the formula:

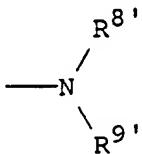


8 in which R^5 is (i) o-phenylene, unsubstituted or sub-
 9 substituted with 1 to 3 substituents each selected indepen-
 10 dently from nitro, cyano, trifluoromethyl, carbethoxy, car-
 11 bomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, car-
 12 boxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy
 13 of 1 to 4 carbon atoms, or halo, or (ii) the divalent
 14 residue of pyridine, pyrrolidine, imidazole, naphthalene,
 15 or thiophene, wherein the divalent bonds are on vicinal
 16 ring carbon atoms;

17 R^6 is $-\text{CO}-$, $-\text{CH}_2-$, or $-\text{SO}_2-$;

18 R^7 is (i) hydrogen if R^6 is $-\text{SO}_2-$, (ii) straight, branched,
 19 or cyclic alkyl of 1 to 12 carbon atoms, (iii) pyridyl,
 20 (iv) phenyl or phenyl substituted with one or more sub-
 21 substituents each selected independently of the other from
 22 nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy,
 23 carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy,
 24 amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10
 25 carbon atoms, or halo, (v) benzyl unsubstituted or
 26 substituted with one to three substituents selected from
 27 the group consisting of nitro, cyano, trifluoromethyl,
 28 carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl,
 29 acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon
 30 atoms, alkoxy of 1 to 4 carbon atoms, or halo,
 31 (vi) napthyl, (vii) benzyloxy, or (viii) imidazol-4-
 32 ylmethyl;

33 R^{12} is $-\text{OH}$, alkoxy of 1 to 12 carbon atoms, $-\text{O}-\text{CH}_2\text{-pyridyl}$,
 34 $-\text{O}-\text{benzyl}$, or



1 where n has a value of 0, 1, 2, or 3;

2 R^{8'} is hydrogen or alkyl of 1 to 10 carbon atoms; and

3 R^{9'} is hydrogen, alkyl of 1 to 10 carbon atoms, -CH₂-
4 pyridyl, benzyl, -COR¹⁰, or -SO₂R¹⁰ in which R¹⁰ is hydro-
5 gen, alkyl of 1 to 4 carbon atoms, or phenyl.

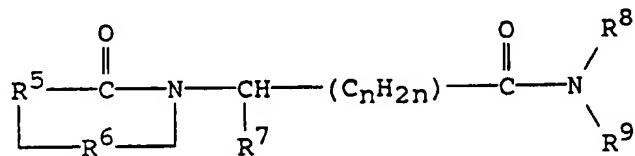
6 27. The compound according to claim 26 which is 3-phthalimido-
7 3-(4-methoxyphenyl)propanamide.

8 28. The compound according to claim 26 which is 3-phthalimido-
9 3-(3,4-dimethoxyphenyl)propanamide.

10 29. The compound according to claim 26 which is 2-phthalimido-
11 3-phenylpropanamide.

12 30. The compound according to claim 26 which is 2-phthalimido-
13 3-(4-hydroxy)phenylpropanamide.

14 31. The method of reducing levels of TNF_α in a mammal which
15 comprises administering thereto an effective amount of a
16 compound of the formula:



23 in which

24 R⁵ is (i) o-phenylene, unsubstituted or substituted with 1
25 to 3 substituents each selected independently from nitro,
26 cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbo-
27 propoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy,
28 amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 car-
29 bon atoms, or halo, or (ii) the divalent residue of pyri-
30 dine, pyrrolidine, imidazole, naphthalene, or thiophene,
31 wherein the divalent bonds are on vicinal ring carbon
32 atoms;

33 R⁶ is -CO-, -CH₂-, or -SO₂-;

1 R⁷ is (i) hydrogen if R⁶ is -SO₂-, (ii) straight, branched,
2 or cyclic alkyl of 1 to 12 carbon atoms, (iii) pyridyl,
3 (iv) phenyl or phenyl substituted with one or more sub-
4 stituents each selected independently of the other from
5 nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy,
6 carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy,
7 amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10
8 carbon atoms, or halo, (v) alkyl of 1 to 10 carbon atoms,
9 (vi) benzyl unsubstituted or substituted with one to three
10 substituents selected from the group consisting of nitro,
11 cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbo-
12 propoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy,
13 amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 car-
14 bon atoms, or halo, (vii) napthyl, (viii) benzyloxy, or
15 (ix) imidazol-4-ylmethyl;
16 n has a value of 0, 1, 2, or 3;

17 R⁸ is hydrogen or alkyl of 1 to 10 carbon atoms; and

18 R⁹ is hydrogen, alkyl of 1 to 10 carbon atoms, -CH₂-
19 pyridyl, benzyl, -COR¹⁰, or -SO₂R¹⁰ in which R¹⁰ is hydro-
20 gen, alkyl of 1 to 4 carbon atoms, or phenyl.

21 32. The method of inhibiting TNF_α-activated retrovirus repli-
22 cation in a mammal which comprises administering thereto an
23 effective amount of a compound according to claim 2.

24 33. The method of inhibiting TNF_α-activated retrovirus repli-
25 cation in a mammal which comprises administering thereto an
26 effective amount of a compound according to claim 10.

27 34. The method of inhibiting TNF_α-activated retrovirus repli-
28 cation in a mammal which comprises administering thereto an
29 effective amount of a compound according to claim 22.

30 35. The method of inhibiting TNF_α-activated retrovirus repli-
31 cation in a mammal which comprises administering thereto an
32 effective amount of a compound according to claim 26.

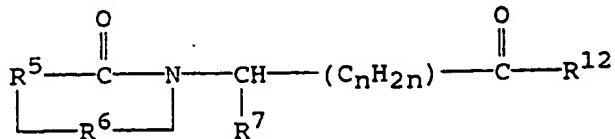
1 36. A pharmaceutical composition comprising an amount of a
2 compound according to claim 2 effective upon single or mul-
3 tiple dosage to inhibit TNF α .

4 37. A pharmaceutical composition comprising an amount of a
5 compound according to claim 10 effective upon single or
6 multiple dosage to inhibit TNF α .

7 38. A pharmaceutical composition comprising an amount of a
8 compound according to claim 22 effective upon single or
9 multiple dosage to inhibit TNF α .

10 39. A pharmaceutical composition comprising an amount of a
11 compound according to claim 26 effective upon single or
12 multiple dosage to inhibit TNF α .

13 40. The method of reducing levels of TNF α in a mammal which
14 comprises administering thereto an effective amount of a
15 compound of the formula:

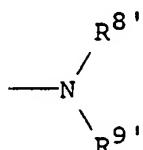


22 in which R⁵ is (i) o-phenylene, unsubstituted or substi-
23 tuted with 1 to 3 substituents each selected independently
24 from nitro, cyano, trifluoromethyl, carbethoxy, car-
25 bomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, car-
26 boxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy
27 of 1 to 4 carbon atoms, or halo, or (ii) the divalent
28 residue of pyridine, pyrrolidine, imidazole, naphthalene,
29 or thiophene, wherein the divalent bonds are on vicinal
30 ring carbon atoms;

31 R⁶ is -CO-, -CH₂-, or -SO₂-;

32 R⁷ is (i) hydrogen if R⁶ is -SO₂-, (ii) straight, branched,
33 or cyclic alkyl of 1 to 12 carbon atoms, (iii) pyridyl,
34 (iv) phenyl or phenyl substituted with one or more sub-
35 stituents each selected independently of the other from
36 nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy,

1 carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy,
2 amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10
3 carbon atoms, or halo, (v) alkyl of 1 to 10 carbon atoms,
4 (vi) benzyl unsubstituted or substituted with one to three
5 substituents selected from the group consisting of nitro,
6 cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbo-
7 propoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy,
8 amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 car-
9 bon atoms, or halo, (vii) napthyl, (viii) benzyloxy, or
10 (ix) imidazol-4-ylmethyl;
11 R¹² is -OH, alkoxy of 1 to 12 carbon atoms, -O-CH₂-pyridyl,
12 -O-benzyl, or



19 n has a value of 0, 1, 2, or 3;
20 R^{8'} is hydrogen or alkyl of 1 to 10 carbon atoms; and
21 R^{9'} is hydrogen, alkyl of 1 to 10 carbon atoms, -CH₂-
22 pyridyl, benzyl, -COR¹⁰, or -SO₂R¹⁰ in which R¹⁰ is hydro-
23 gen, alkyl of 1 to 4 carbon atoms, or phenyl.

24 41. The process of claim 1 wherein the step of refluxing is
25 performed in the presence of a base.

26 42. The compound according to claim 26 wherein:

27 R⁵ is o-phenylene;
28 R⁶ is -CO-;
29 R⁷ is (i) straight, branched or cyclic alkyl of 6-9 or 11-
30 12 carbon atoms; (ii) pyridyl, (iii) phenyl substituted
31 with cyano, trifluoromethyl, carbethoxy, carbomethoxy,
32 carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy,
33 alkyl of 2 to 10 carbon atoms, alkoxy of 1 to 10 carbon
34 atoms, or halo, (iv) phenyl substituted with 2 or more
35 substituents each selected independently of the other from
36 nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy,
37 carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy,

1 amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10
2 carbon atoms, or halo, (v) benzyl unsubstituted or
3 substituted with 1 to 3 substituents selected from the
4 group consisting of nitro, cyano, trifluoromethyl,
5 carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl,
6 acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon
7 atoms, alkoxy of 1 to 4 carbon atoms, or halo, (vi)
8 naphthyl, (vii) benzyloxy, (viii) or (ix) imidazol-4-
9 ylmethyl;
10 R¹² is methoxy; and
11 where n has a value of 1.

12 43. The compound according to claim 26 wherein:

13 R⁵ is o-phenylene;
14 R⁶ is -CO-;
15 R⁷ is (i) straight, branched or cyclic alkyl of 5 to 12
16 carbon atoms, (ii) pyridyl, (iii) phenyl substituted with
17 cyano, trifluoromethyl, carbethoxy, carbomethoxy,
18 carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy,
19 amino, alkyl of 1 to 10 carbon atoms, alkoxy of 2 to 10
20 carbon atoms, or halo, (iv) phenyl substituted with 2 or
21 more substituents each selected independent of the other
22 from nitro, cyano, trifluoromethyl, carbethoxy,
23 carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy,
24 carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms,
25 alkoxy of 1 to 10 carbon atoms, or halo, (v) benzyl
26 substituted with 1 to 3 substituents selected from the
27 group consisting of nitro, cyano, trifluoromethyl,
28 carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl,
29 acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon
30 atoms, alkoxy of 1 to 4 carbon atoms, or halo, (vi)
31 naphthyl, (vii) benzyloxy, or (viii) imidazol-4-ylmethyl;
32 R¹² is -OH; and
33 where n has a value of 1.

1 44. The compound according to claim 26 wherein:

2 R⁵ is o-phenylene;
3 R⁶ is -CO-;
4 R⁷ is (i) straight, branched or cyclic alkyl of 1 to 12
5 carbon atoms, (ii) pyridyl, (iii) phenyl or phenyl
6 substituted with cyano, trifluoromethyl, carbethoxy,
7 carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy,
8 carboxy, hydroxy, alkyl of 1 to 10 carbon atoms, alkoxy of
9 2 to 10 carbon atoms, or halo, (iv) phenyl substituted with
10 2 or more substituents each selected independent of the
11 other from nitro, cyano, trifluoromethyl, carbethoxy,
12 carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy,
13 carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms,
14 alkoxy of 1 to 10 carbon atoms, or halo, (v) benzyl
15 substituted with 1 to 3 substituents selected from the
16 group consisting of nitro, cyano, trifluoromethyl,
17 carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl,
18 acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon
19 atoms, alkoxy of 1 to 4 carbon atoms, or halo, (vi)
20 naphthyl, (vii) benzyloxy, or (viii) imidazol-4-ylmethyl;
21 R¹² is ethoxy; and
22 where n has a value of 1.

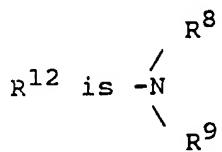
23 45. The compound according to claim 26 wherein:

24 R⁸
25 R¹² is -N /
26 \ R⁹
27
28
29 where R⁸ is hydrogen or alkyl of 1 to 10 carbon atoms;
30 R⁹ is hydrogen, alkyl of 1 to 10 carbon atoms, -CH₂-
31 pyridyl, benzyl, -COR¹⁰, or -SO₂R¹⁰ in which R¹⁰ is
32 hydrogen, alkyl of 1 to 10 carbon atoms, or phenyl.
33

34 46. The compound according to claim 26 wherein:

35 R⁵ is o-phenylene;
36 R⁶ is -CO-;

1 R⁷ is (i) straight, branched or cyclic alkyl of 1 to 12
2 carbon atoms, (ii) pyridyl, (iii) phenyl or phenyl
3 substituted with one or more substituents each selected
4 independent of the other from nitro, cyano,
5 trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy,
6 acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl
7 of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or
8 halo, (v) benzyl unsubstituted or substituted with 1 to 3
9 substituents selected from the group consisting of nitro,
10 cyano, trifluoromethyl, carbethoxy, carbomethoxy,
11 carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy,
12 amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4
13 carbon atoms, or halo, (vi) naphthyl, (vii) benzyloxy, or
14 (viii) imidazol-4-ylmethyl;



23 where R^8 is hydrogen or alkyl of 1 to 10 carbon atoms;
24 R^9 is hydrogen, alkyl of 1 to 10 carbon atoms, $-CH_2-$
25 pyridyl, benzyl, $-COR^{10}$, or $-SO_2R^{10}$ in which R^{10} is
26 hydrogen, alkyl of 1 to 10 carbon atoms, or phenyl; and
27 where n has a value of 1.

28 47. The compound according to claim 26 wherein, R^5 is amino
29 substituted o-phenylene.

30 48. The compound according to claim 26 which is 3-(amino-
31 phthalimido)-3-(3,4-dimethoxyphenyl)propanamide.

32 49. The compound according to claim 26 which is 3-(amino-
33 phthalimido)-3-(3,4-diethoxyphenyl)propanamide.

34 50. The compound according to claim 26 which is methyl [3-
35 phthalimido-3-(3,4-dimethoxyphenyl)]propionate.

36 51. The compound according to claim 26 which is methyl [3-
37 phthalimido-3-(3,4-diethoxyphenyl)]propionate.

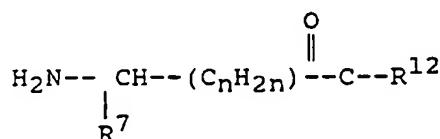
1 52. The compound according to claim 26 which is methyl [3-
2 (amino-phthalimido)-3-(3,4-dimethoxyphenyl)]propionate.

3 53. The compound according to claim 26 which is methyl [3-
4 (amino-phthalimido)-3-(3,4-diethoxyphenyl)]propionate.

5 54. The compound according to claim 26 wherein,
6 R^{12} is -O-methyl.

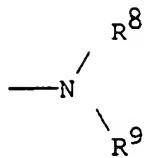
7 55. The compound according to claim 26 wherein,
8 R^6 is - CH_2 -.

9 56. A compound of the formula:



in which

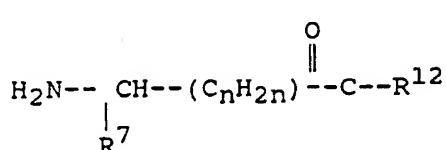
18 R⁷ is (i) straight, branched, or cyclic alkyl of 1 to 12
19 carbon atoms; (ii) pyridyl; (iii) phenyl or phenyl
20 substituted with one or more substituents each selected
21 independently of the other from nitro, cyano,
22 trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy,
23 acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl
24 of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or
25 halo; (iv) benzyl or benzyl substituted with one to three
26 substituents selected from the group consisting of nitro,
27 cyano, trifluoromethyl, carbethoxy, carbomethoxy,
28 carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy,
29 amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4
30 carbon atoms, or halo; (v) naphthyl; (vi) benzyloxy; or
31 (vii) imidazol-4-ylmethyl;
32 R¹² is alkoxy of 1 to 12 carbon atoms, -O-CH₂-pyridyl, -O-
33 benzyl, or
34



R^8 is hydrogen or alkyl of 1 to 10 carbon atoms;

R^9 is hydrogen, alkyl of 1 to 10 carbon atoms, $-COR^{10}$, or $-SO_2R^{10}$ in which R^{10} is hydrogen, alkyl of 1 to 4 carbon atoms, or phenyl.

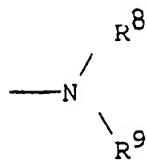
57. The method of reducing levels of TNF α in a mammal which comprises administering thereto an effective amount of a compound of the formula:



in which

R^7 is (i) straight, branched, or cyclic alkyl of 1 to 12 carbon atoms; (ii) pyridyl; (iii) phenyl or phenyl substituted with one or more substituents each selected independently of the other from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo; (iv) benzyl or benzyl substituted with one to three substituents selected from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo; (v) naphthyl; (vi) benzyloxy; or (vii) imidazol-4-ylmethyl;

R^{12} is alkoxy of 1 to 12 carbon atoms, $-O-CH_2$ -pyridyl, $-O-$ benzyl, or



7 where, R^8 is hydrogen or alkyl of 1 to 10 carbon atoms; R^9
8 is hydrogen, alkyl of 1 to 10 carbon atoms, $-\text{COR}^{10}$, or $-\text{SO}_2\text{R}^{10}$; and, R^{10} is Hydrogen, alkyl of 1 to 4 carbon
9 atoms, or phenyl.

10
11 58. The method of inhibiting $\text{TNF}\alpha$ -activated retrovirus
12 replication in a mammal which comprises administering
13 thereto an effective amount of a compound according to
14 claim 57.

15 59. A pharmaceutical composition comprising an amount of a
16 compound according to claim 57 effective upon single or
17 multiple dosage to inhibit $\text{TNF}\alpha$.

18 60. The compound according to claim 26 which is 3-phthalimido-
19 3-(3,4-diethoxyphenyl)propanamide.

20 61. The compound of claim 26 wherein,

21 R^5 is o-phenylene unsubstituted or substituted with 1 to 3
22 substituents each selected independently from nitro, cyano,
23 trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy,
24 acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl
25 of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or
26 halo; and,
27 R^6 is $-\text{CH}_2-$.

28 62. The compound of claim 26 wherein,

29 R^5 is o-phenylene unsubstituted or substituted with 1 to 3
30 substituents each selected independently from nitro, cyano,
31 trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy,
32 acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl
33 of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or
34 halo; and,

1 R¹² is -O-methyl.

2 63. The compound of claim 26 wherein,

3 R⁶ is -CH₂-; and,
4 R¹² is -O-methyl.

5 64. The compound of claim 26 wherein,

6 R⁵ is o-phenylene unsubstituted or substituted with 1 to 3
7 substituents each selected independently from nitro, cyano,
8 trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy,
9 acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl
10 of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or
11 halo;

12 R⁶ is -CH₂-; and,
13 R¹² is -O-methyl.

**CORRECTED
VERSION***

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶:</p> <p>C07D 401/04, 471/04, A61K 31/33 C07D 211/88, 209/48, 403/06, 209/46, 213/55, C07C 229/34, 401/06, 209/76</p>		A3	<p>(11) International Publication Number: WO 95/01348</p> <p>(43) International Publication Date: 12 January 1995 (12.01.95)</p>
<p>(21) International Application Number: PCT/US94/07411</p> <p>(22) International Filing Date: 1 July 1994 (01.07.94)</p> <p>(30) Priority Data: 08/087,510 2 July 1993 (02.07.93) US</p> <p>(71) Applicant (for all designated States except US): CELGENE CORPORATION [US/US]; 7 Powder Horn Drive, Warren, NJ 07059 (US).</p> <p>(71)(72) Applicant and Inventor: MULLER, George, W. [US/US]; 250 Windmill Court, Bridgewater, NJ (US).</p> <p>(74) Agents: NISSIM, Stuart, H. et al.; Mathews, Woodbridge & Collins, Suite 306, 100 Thanet Circle, Princeton, NJ 08540-3662 (US).</p>		<p>(81) Designated States: AU, CA, CZ, FI, HU, JP, KR, NZ, PL, RU, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> <p>(88) Date of receipt of the international search report: 9 March 1995 (09.03.95)</p>	
<p>(54) Title: IMIDES AS INHIBITORS OF TNF ALPHA</p> <p>(57) Abstract</p> <p>Cyclic imides are inhibitors of tumor necrosis factor α and can be used to combat cachexia, endotoxic shock, and retrovirus replication. A typical embodiment is methyl [3-phthalimido-3-(3,4-dimethoxyphenyl)]propionate.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/US 94/07411

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/04 C07D471/04 A61K31/33 C07D211/88 C07D209/48
C07D403/06 C07D209/46 C07D213/55 C07C229/34 C07D401/06
C07D209/76

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOURNAL OF PHARMACEUTICAL SCIENCES, vol.57, no.5 pages 757 - 764 SHEALY Y.F. ET AL. 'Synthesis of D- and L-thalidomide and related studies' * page 763 : N,N'-carbonyldiimidazole method * ---	1
A	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol.82, 5 September 1960, WASHINGTON, DC US pages 4596 - 4600 R. PAUL ET AL. 'N,N'-Carbonyldiimidazole, a new peptide forming reagent.' * page 4597, right column, second half - page 4598, table I * --- -/-	1

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

2

Date of the actual completion of the international search

Date of mailing of the international search report

8 November 1994

14.02.95

Name and mailing address of the ISA
European Patent Office, P.B. 5818 PatentUaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Van Bijlen, H

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 94/07411

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB,A,768 821 (CHEMIE GRÜNENTHAL GMBH) 20 February 1957 * complete document * ---	1
A	US,A,4 918 193 (ST. R. BURZYNSKI) 17 April 1990 * column 2 * -----	1

2

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 94/07411

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. Claims 1 and 41
2. Claims 2-25, 32-34, 36-38
3. Claims 26-31, 35, 39, 40, 42-55, 60-64
4. Claims 56-59

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1 and 41

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 94/07411

Patent document cited in search report	Publication date	Patent family member(s)		Publication date	
GB-A-768821		NONE			
US-A-4918193	17-04-90	FI-B-	92391	29-07-94	
		PL-B-	163552	29-04-94	
		SU-A-	1809830	15-04-93	